SGGD

9th Meeting of the Study Group on Genetics of Diabetes

EXETER 17-19TH APRIL 2024

#SGGDExeter2024

University of Exeter

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Contents

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Programme

SGGD
9th Meeting of the Study Group on Genetics of Diabetes
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Full programme

Wednesday 17th April – Friday 19th April 2023
Peter Chalk Centre, University of Exeter, Stocker Rd, Exeter EX4 4QD

Wednesday 17th April

12:00 – 13:15	**Lunch + Registration**
13:15 – 13:30	Welcome and opening address (Andrew Hattersley)
13:30 – 15:00	**Invited session 1- Using common genetic variants to diagnose and understand disease across ancestries** *Chairs – Tim Frayling (Geneva) and Miriam Udler (Boston)*
13:30 – 14:00	Diagnosis and prediction of Type 1 diabetes (Richard Oram, Exeter)
14:00 – 14:30	African genomes hold the key to accurate genetic risk prediction (Segun Fatumo, LSHTM)
14:30 – 15:00	Applying Mendelian Randomization in obesity (George Davey Smith, Bristol)
15:00 – 15:30	**Coffee Break**
15:30 – 16:30	**Abstract selected oral presentation session 1** *Chairs Inês Barroso (Exeter) and Jose Florez (Boston)*
15:30 – 15:45	Polygenic risk scores for the prediction of type 2 diabetes and complications in diverse ancestries (Alicia Huerta-Chagoya, MGH/Broad)
15:45 – 16:00	A South Asian-specific missense variant in PIEZO1 may distort relationships between HbA1c and blood glucose (Miriam Samuel, QMUL)
16:00 – 16:15	Identifying rare non-coding regulatory regions for HbA1c using Whole Genome Sequences (Gareth Hawkes, Exeter)
16:15 – 16:30	Rare variant associations with birth weight highlight genetic links with later metabolic health (Robin Beaumont, Exeter)
16:30 – 16:45	**Break**
16:45 - 17:45	**Keynote –** Telomere to telomere human genomes and improved genotyping of complex structural variation (Evan Eichler, Washington)
17:45 – 19:00	**Drinks Reception and poster viewing**

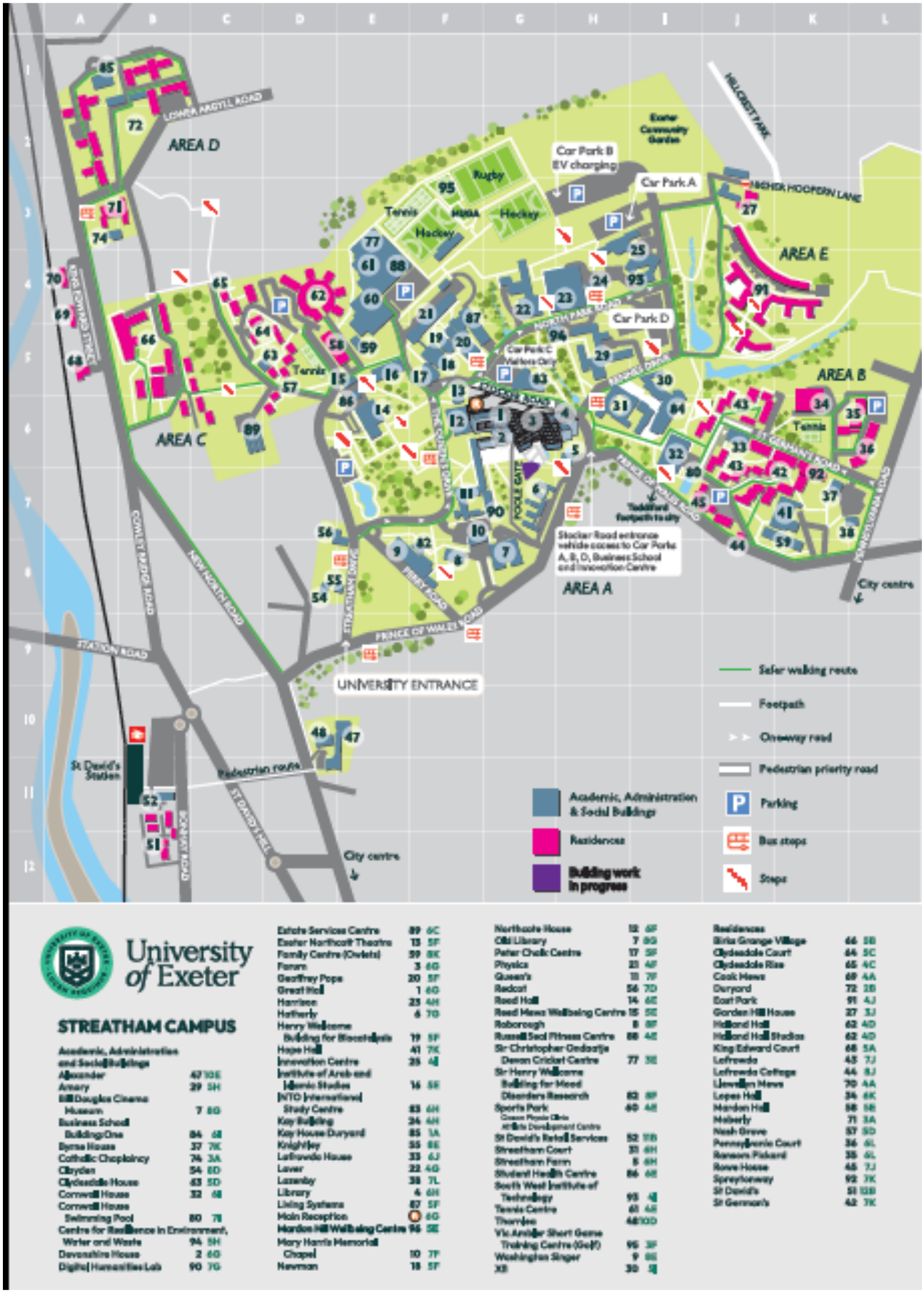
Thursday 18th April

09:00 – 10:30	**Invited session 2 – What's new in monogenic gene discovery** *Chairs – Pal Njølstad (Bergen) and Sadia Saeed (Lille)*
09:00 – 09:30	Gene discovery in neonatal diabetes to understand beta-cell biology (Elisa De Franco, Exeter)
09:30 – 10:00	From gene discovery to mechanism (Miriam Cnop, Brussels)
10:00 – 10:15	Protein-truncating variants in BSN are associated with severe adult-onset obesity, type 2 diabetes and fatty liver disease (Yajie Zhao, Cambridge)
10:30 – 11:00	**Highly Commended Poster Flash Talks**
11:00 – 12:15	**Poster session and Coffee**
12:15 - 12:30	**Sponsor talk -** Oxford Nanopore Technologies
12:30 – 13:15	**Lunch**
13:15 – 14:45	**Invited session 3 – From variant to function** *Chairs – Jorge Ferrer (Barcelona) and Endrina Mujica (Uppsala)*
13:15 – 13:45	Translational Genomics of Type 2 Diabetes (Ele Zeggini, Germany)
13:45 – 14:15	Linking metabolic disease polygenic scores to disease biology (Melina Claussnitzer, Boston (MGH/Broad))
14:15 – 14:45	What can we learn from stem cell derived islets? (Timo Otonkoski, Helsinki)
14:45 – 15:30	**Abstract selected Oral Session 2** *Chairs – Emma Ahlqvist (Lund) and Inga Prokopenko (Surrey)*
14:45 – 15:00	Ultra-deep targeted transcriptome sequencing identifies isoform diversity across human pancreatic development (Ailsa MacCalman, Exeter)
15:00 – 15:15	Age-related DNA methylation dynamics in insulin-sensitive tissues and their implications in metabolic health and obesity (Amna Khamis, Lille)
15:15 – 15:30	Unravelling the interplay between type 2 diabetes, genetics and metabolite levels (Ozvan Bocher, Munich)
15:30 – 15:45	Genetic architecture of oral glucose-stimulated insulin release provides biological insights into type 2 diabetes aetiology (Anne Madsen, Copenhagen)
15:45 – 16:15	**Coffee Break**
16:15 – 17:15	**Abstract selected Oral Session 3** *Chairs – Cecile Saint-Martin (Paris) and Antonio Cuesta (Malaga)*
16:15 – 16:30	Homozygous mutations in SREK1 linked to a new condition of syndromic obesity (Sadia Saeed, Lille)
16:30 – 16:45	Disease-causing low-level mosaic variants can be detected in blood samples from individuals with hyperinsulinism (Tom Laver, Exeter)
16:45 – 17:00	From 58 type-2 diabetes candidate genes to 5: A validated 2-step in vivo prioritization system (Endrina Mujica, Uppsala)
17:00 – 17:15	Homozygous and Heterozygous INS Mutations Cause Divergent Clinical and iPSC-Derived β-Cell Phenotypes (Yue Tong, Brussels)
19:00	**Reception dinner + live music** Holland Hall, University of Exeter, Clydesdale Road, Exeter, EX4 4SA **Dinner talk - Tom Staniford**

Friday 19th April

09:00 – 10:30	**Session 4 – Lessons from other diseases and technologies** *Chairs – Torben Hansen (Copenhagen) and Daniela Gašperíková (Slovakia)*
09:00 – 09:30	Finding new diagnoses in the Deciphering Developmental Disorders Study (Caroline Wright, Exeter)
09:30 – 10:00	Genetics and Genomics in Drug Discovery and Development (Rob Scott, GSK)
10:00 – 10:30	Epigenetic and transcriptional pathways to brain disease (Jon Mill, Exeter)
10:30 – 11:00	**Coffee Break with Traditional Devon Cream Tea**
11:00 – 13:00	**Session 5 – Translating genetics to the clinic** *Chairs – Tiinamaija Tuomi (Helsinki) and Leen 't Hart (Leiden)*
11:00 – 11:30	Precision medicine in diabetes (Ewan Pearson, Dundee)
11:30 – 12:00	Are genetic diabetes clusters ready for the clinic? (Miriam Udler, Boston)
12:00 – 12:30	The impact of rare variants in common diabetes and obesity towards precision medicine (Amélie Bonnefond, Lille)
12:30 – 13:00	**Oral and poster awards + closing remarks**
13:00 – 14:15	**Lunch & Meeting close**

Campus Map



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STREATHAM CAMPUS

Academic, Administration and Social Buildings

Alexander	47	10E
Amory	29	5H
Bill Douglas Cinema Museum	7	8G
Business School Building/One	84	6E
Byrne House	37	7K
Catholic Chaplaincy	74	3A
Clayden	54	6D
Clydesdale House	43	5D
Cornwall House	32	6E
Cornwall House Swimming Pool	80	7E
Centre for Resilience in Environment, Water and Waste	94	5H
Devonshire House	2	6G
Digital Humanities Lab	90	7G
Estate Services Centre	89	6C
Exeter Northcott Theatre	13	5F
Family Centre (Owlets)	59	8K
Forum	3	6G
Geoffrey Pope	20	5F
Great Hall	1	6G
Harrison	23	4H
Hatherly	6	7G
Henry Wellcome Building for Biocatalysis	19	5F
Hope Hall	41	7K
Innovation Centre	25	4E
Institute of Arab and Islamic Studies	16	5E
INTO International Study Centre	83	6H
Kay Building	24	6H
Kay House Duryard	85	1A
Knightley	55	8E
Lafrowda House	33	6J
Laver	22	4G
Lazenby	38	7L
Library	4	6H
Living Systems	87	5F
Main Reception	0	6G
Mardon Hall Wellbeing Centre	96	5E
Mary Harris Memorial Chapel	10	7F
Newman	18	5F
Northcote House	12	6F
Old Library	7	8G
Peter Chalk Centre	17	5F
Physics	21	4F
Queen's	11	7F
Redcat	56	7D
Reed Hall	14	6E
Reed Hall Wellbeing Centre	15	5E
Roborough	8	8F
Russell Seal Fitness Centre	88	4E
Sir Christopher Ondaatje Devon Cricket Centre	77	3E
Sir Henry Wellcome Building for Mood Disorders Research	82	8F
Sports Park	60	4E
St David's Retail Services	52	11B
Streatham Court	31	6H
Streatham Farm	5	6H
Student Health Centre	86	6E
South West Institute of Technology	93	4J
Tennis Centre	61	4E
Thornlea	48	10D
Vic Ambler Short Game Training Centre (Golf)	95	3F
Washington Singer	9	8E
XB	30	5J

Residences

Birks Grange Village	66	2B
Clydesdale Court	64	5C
Clydesdale Rise	65	4C
Cook Mews	69	4A
Duryard	72	2B
East Park	91	4J
Garden Hill House	27	3J
Holland Hall	62	4D
Holland Hall Studios	62	4D
King Edward Court	68	5A
Lafrowda	45	7J
Lafrowda Cottage	44	8J
Llewellyn Mews	70	4A
Lopes Hall	34	6K
Mardon Hall	58	8E
Moberly	71	3A
Nash Grove	57	9D
Pennsylvania Court	36	6L
Ransom Pickard	35	6L
Rowe House	46	7J
Spreyfoneway	92	7K
St David's	51	12B
St Germain's	42	7K

Invited Speakers

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Dr Richard Oram

University of Exeter

Invited talk

Diagnosis and prediction of Type 1 diabetes

Wednesday 17th April 13:30 – 14:00

He is a clinician scientist with a record in bringing original ideas and approaches to type 1 diabetes research. His contributions include paradigm-shifting studies of β-cell function, highlighting persistence of endogenous insulin in many with longstanding type 1 diabetes (T1D). Dr. Oram developed a type 1 diabetes genetic risk score (T1D GRS) that has rapidly been integrated into clinical care for classification of diabetes, with potential field changing impacts on type 1 diabetes population screening. In parallel, his study of extremely early onset T1D in babies is revealing novel insights about genetic, immune and phenotypic factors associated with very early onset diabetes, with critical advances relating to the role of β-cell stress, and immune checkpoints in causality of autoimmunity. He has numerous national and international collaborations translating these findings across the globe.

Dr Oram will discuss polygenic scores for type 1 diabetes and their role in both prediction and classification of type 1 diabetes. In line with the title of the session Dr Oram will talk about advances related to the study and prediction of type 1 diabetes by diverse ancestry and geography. Importantly outlining some of the challenges and knowledge gaps, and some features of the genetic architecture of HLA linked disease that are different from other common complex diseases, and may impact application of trans-ancestry scores.

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Prof. Segun Fatumo

Queen Mary University of London & MRC Uganda

Invited talk

How do genetic risk scores translate across ancestries

Wednesday 17th April 14:00

Segun Fatumo is Professor and Chair of Genomic Diversity at Queen Mary University of London and the head of NCD Genomics at the MRC Uganda. He specialises in Genomics and other Omics of African Populations using approaches such as Genome-wide association studies (GWAS), Polygenic Risk Score Analysis (PRS) and Mendelian Randomisation (MR). He co-led the first major GWAS of cardiometabolic traits in Africa and led the first GWAS of Kidney functions in continental African populations. Segun Fatumo is co-director of the KidneyGenAfrica Research Partnership Programme - A Partnership to Deliver Research and Training Excellence in Genomics of Kidney Disease in Africa. Segun Fatumo is strongly committed to increasing diversity in genomic studies and was recently awarded the prestigious MRC Impact prize for advocating for the inclusion of Africa in genomic research and championing genetic risk prediction of complex diseases in Africa.

The majority of polygenic risk scores have been generated and optimized in people of European ancestry to predict complex traits and disease risk. Since PRS are frequently based on genome-wide association studies (GWAS), the overrepresentation of European populations in GWAS hampers the applicability of PRS to other ancestries and thus limits the implementation of PRS in genomic medicine. Given that Africa is the origin of modern humans, African populations possess a greater degree of genetic diversity than any other continent, and the genetic diversity found in non-Africans is largely a subset of that found in Africa. Despite being humanity's origin and its corresponding significance for genomic studies, Africa lags behind in genomic research, with nearly nine out of ten genomic studies conducted on people of European descent and only 1.1% genomic studies on people of African descent. Therefore, excluding Africa's populations and their genetic diversity will continue to weaken the accuracy and transferability of PRS. In my presentation, I will demonstrate how we achieve more accurate genetic risk prediction and transferability using large-scale African data.

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Prof. George Davey Smith

University of Bristol

Invited talk

Applying Mendelian Randomization in obesity

Wednesday 17th April 14:30

George Davey Smith was a member of the noise-terrorism outfit Scum Auxiliary in the early 1980s. Since artistic and commercial success eluded them, he has had to earn his living working as an epidemiologist in the provinces.

Mendelian randomization (MR) has been extensively used to study the influence of obesity on health outcomes. I will review the approach and some applications, including those relating to body size at difference stages of lifecourse. I will discuss limitations of the approach, and highlight some erroneous conclusions that have been drawn from MR studies. I will finish on some possible future directions.

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Prof. Evan Eichler

Howard Hughes Medical Institute & University of Washington

Invited talk

Telomere to telomere human genomes and improved genotyping of complex structural variation

Wednesday 17th April 16:45

Evan Eichler is a Professor of Genome Sciences and Howard Hughes Medical Institute Investigator. He received his Ph.D. from Baylor College of Medicine. After his postdoctoral fellowship at Lawrence Livermore National Laboratory, he joined Case Western Reserve University in 1997 and the University of Washington in 2004. His research group provided the first genome-wide view of segmental duplications within human and primate genomes. He is a leader in identifying and sequencing normal and disease-causing structural variation in the human genome. The long-term goal of his research is to understand the evolution and mechanisms of recent gene duplication and its relationship to copy number variation and human disease with a specific emphasis on the genetic architecture of autism and neurodevelopmental delay.

The discovery and resolution of genetic variation is critical to understanding disease and disease susceptibility. I will present our most recent work sequencing diverse human genomes telomere-to-telomere (T2T) using both ultra-long and high-fidelity long-read sequencing technologies. The approach allows us to sequence, assemble, and phase all forms of human genetic variation, including complex structural and copy-number variants irrespective of size—the vast majority of which are not routinely characterized by short-read sequencing. Advances in this area have made possible the first T2T assemblies of human genomes, the development of a pangenome reference, and new biological insights into regions typically excluded from human genetic studies. I will highlight how these data are being used to improve short-read genotyping and its potential to characterize complex genetic variation and improve disease associations both directly and indirectly. Assembly-based variant discovery has the potential to provide a complete understanding of human genetic variation at every level and, we predict, will be the future of genetic and clinical-based research.

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Dr. Elisa De-Franco PhD

University of Exeter

Invited talk

Gene discovery in neonatal diabetes to understand beta-cell biology

Thursday 18th April 9:00

Elisa studied medical biotechnologies at the University of Turin, Italy, followed by a prestigious EU framework-Marie Curie PhD fellowship at the University of Exeter. She is currently a Senior Research Fellow in Exeter and the recipient of a Diabetes UK RD Lawrence Fellowship and an EFSD/Novo Nordisk Future Leader award.

Elisa's research uses genome sequencing to discover genes essential for beta-cell development and function. Her work has been recognised by multiple awards, including the EASD Rising Star award in 2018, the ISPAD Young Investigator Award in 2020, and the Genes Young Investigator Award in Human Genomics and Genetic Diseases in 2022. She has contributed to the discovery of over 10 novel genetic causes of neonatal diabetes and published over 90 papers, including first-author publications in the Lancet and Nature Genetics

Understanding the mechanisms essential for human pancreatic beta-cells development and function is essential to improve our understanding of how type 1 and type 2 diabetes develop. Identifying the rare, single gene variants which result in individuals developing diabetes in the first 6 months of life (neonatal diabetes) can provide unique insights into the genes essential for human beta-cells.

The advent of next-generation sequencing over a decade ago has allowed genetic discovery approaches in neonatal diabetes to search for novel genetic causes of the disease, without relying on previous knowledge of a gene's function within the beta-cells. By performing whole genome sequencing analysis of >130 individuals with neonatal diabetes, we have identified pathogenic variants in genes which were not previously thought to be important within beta-cells. These include genes essential for beta-cell survival through regulation of endoplasmic reticulum stress, as well as genes crucial for human pancreatic development (such as the primate-specific gene ZNF808).

These discoveries highlight the power of human genetic studies to pinpoint genes essential for human beta-cell development and survival, improving our understanding of the cellular mechanisms leading to diabetes. This new knowledge could be essential to inform the development of novel therapies for individuals living with diabetes.

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Prof. Miriam Cnop MD PhD

University of Brussels

Invited talk

From gene discovery to mechanism

Thursday 18th April 9:30

Miriam Cnop obtained MD and PhD degrees at Vrije Universiteit Brussel and trained as a postdoctoral fellow at University of Washington, Seattle. She currently directs the ULB Center for Diabetes Research and works as a diabetologist in ULB Erasmus Hospital. She studies the mechanisms of human beta cell failure in the pathogenesis of type 2 and monogenic diabetes, with a particular interest in endoplasmic reticulum (ER) stress. To gain insight into pathways of beta cell failure and test novel therapies, she established an induced pluripotent stem cell (iPSC) laboratory, in which patients' iPSCs are differentiated into beta cells. She coordinated the European Horizon 2020 project T2DSystems in which >500 human islet datasets were compiled in TIGER (Translational human pancreatic Islet Genotype tissue-Expression Resource, http://tiger.bsc.es) enabling eQTL and other analyses to interrogate the genetic and molecular etiology of beta cell failure in diabetes.

Diabetes is a heterogeneous disorder, with diverse routes leading to pancreatic beta cell failure. Genetic and lifestyle factors play essential roles in polygenic diabetes. We identified ER stress as a cellular response contributing to fatty acid-induced beta cell failure in type 2 diabetes. Saturated fatty acids impair ER-to-Golgi protein trafficking and induce signaling in the PERK branch of the ER stress response, thereby triggering beta cell demise.

Monogenic forms of diabetes are simpler systems, and unambiguously reveal genes that are essential for beta cell development, function and/or survival. More than a dozen monogenic forms of diabetes have been described that are caused by mutations in genes of the ER stress response. Five pertain to the PERK branch, providing strong human genetic evidence for the importance of PERK signaling in maintaining beta cell integrity. In these diseases, dysregulated eIF2□ phosphorylation and mRNA translation lead to beta cell demise. Three monogenic forms of diabetes are caused by perturbations in the ER-to-Golgi protein trafficking pathway. The differentiation of patients' iPSCs into beta cells provides an exciting disease-relevant model to study molecular mechanisms of beta cell failure and test beta cell protective therapies.

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Dr Yajie Zhao

University of Cambridge

Invited talk

Protein-truncating variants in BSN are associated with severe adult-onset obesity, type 2 diabetes and fatty liver disease

Thursday 18th April 10:00

Dr Yajie Zhao is an MRC Postdoctoral Fellow at the University of Cambridge, where he obtained his PhD. His research focuses on linking diseases and phenotypes, especially clonal hematopoiesis and metabolic related phenotypes, to their genetic causes using data from large cohorts. He was the postdoctoral finalist for the 2023 Trainee Awards for Excellence in Human Genetics Research for the 2023 Annual Meeting of the ASHG. He was selected to give a platform talk at the 2022 ASHG, a plenary talk at the 2023 ASHG. He also founded the Human Genetics Network, a professional network for researchers in related areas.

Obesity is a major risk factor for many common diseases and has a substantial heritable component. To identify new genetic determinants, we performed exome-sequence analyses for adult body mass index (BMI) in up to 587,027 individuals. We identified rare loss-of-function variants in two genes (BSN and APBA1) with effects substantially larger than those of well-established obesity genes such as MC4R. In contrast to most other obesity-related genes, rare variants in BSN and APBA1 were not associated with normal variation in childhood adiposity. Furthermore, BSN protein-truncating variants (PTVs) magnified the influence of common genetic variants associated with BMI, with a common variant polygenic score exhibiting an effect twice as large in BSN PTV carriers than in noncarriers. Finally, we explored the plasma proteomic signatures of BSN PTV carriers as well as the functional consequences of BSN deletion in human induced pluripotent stem cell-derived hypothalamic neurons. Collectively, our findings implicate degenerative processes in synaptic function in the etiology of adult-onset obesity.

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Prof. Eleftheria Zeggini

Institute of Translational Genomics, Helmholtz Munich

Invited talk

Translational Genomics of Type 2 Diabetes

Thursday 18th April 13:15

Eleftheria Zeggini is the founding Director of the Institute of Translational Genomics at Helmholtz Munich and holds the TUM Liesel Beckmann Distinguished Professorship at the Technical University Munich School of Medicine. Her research leverages big biomedical data to translate insights from genomics into mechanisms of disease development and progression, shortening the path to translation and empowering precision medicine.

Type 2 diabetes (T2D) is a heterogeneous disease that develops through diverse pathophysiological processes and molecular mechanisms that are often specific to cell type. To characterize the genetic contribution to these processes across ancestry groups, we have aggregated genome-wide association study (GWAS) data from 2,535,601 individuals (39.7% not of European ancestry), including 428,452 cases of T2D. We identify 1,289 independent association signals at genome-wide significance ($P < 5 \times 10{-}8$) that map to 611 loci, of which 145 loci are previously unreported. We define eight non-overlapping clusters of T2D signals that are characterized by distinct profiles of cardiometabolic trait associations. We build cluster-specific partitioned polygenic scores in a further 279,552 individuals of diverse ancestry, including 30,288 cases of T2D, and test their association with T2D-related vascular outcomes. Cluster-specific partitioned polygenic scores are associated with coronary artery disease, peripheral artery disease and end-stage diabetic nephropathy across ancestry groups, highlighting the importance of obesity-related processes in the development of vascular outcomes.

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Melina Claussnitzer, PhD

Massachusetts General Hospital Harvard Medical School, Broad Institute of MIT and Harvard

Invited talk

Linking metabolic disease polygenic scores to disease biology

Thursday 18th April 13:45

Melina Claussnitzer is an institute member at the Broad Institute of MIT and Harvard, and an associate professor at Massachusetts General Hospital and Harvard Medical School (HMS). She also co-directs the Type 2 Diabetes Systems Genomics Initiative at the Broad, and serves as the associate director of scientific strategy for the Novo Nordisk Foundation Center for Genomic Mechanisms of Disease at the Broad. Her lab focuses on the conversion of disease-associated genetic variants to function (V2F) and, more specifically, on the dissection of the genetic basis of type 2 diabetes and its comorbidities into molecular and cellular programs as actionable therapeutic strategies.

Claussnitzer's research program spans a diversity of areas in the field of disease genomics, and involves a combination of experimental and computational strategies to discover pathophysiological targets underlying the genetic risk of metabolic disease phenotypes. Claussnitzer earned her "Vordiplom" (equivalent of B.Sc.) in mathematics and nutritional sciences and her "Diplom" (equivalent of M.Sc.) in molecular biology and nutritional sciences from the University of Hohenheim, Germany. She earned her Ph.D. in genetics of complex diseases from the Technical University of Munich, Germany. After her postdoctoral fellowship at the Institute of Ageing Research at Beth Israel Deaconess Medical Center, Harvard Medical School she started her lab at the Broad Institute as a faculty member at Harvard Medical School and an adjunct faculty at the Computer Science and Artificial Intelligence Lab at MIT.

The Claussnitzer team is enthusiastic about adding function to large-scale genetic association study results (Variant-to-Function, V2F) in the context of metabolic disease. The motivation of our research program has been that those genetic studies succeeded in identifying more than 1,000 associations between genetic loci and metabolic disease in humans. Yet, the next grand challenge — systematically dissecting the mechanisms by which these variants affect disease — has still to be solved and scaled. We have previously developed V2F frameworks for going from variants to genes to cells to biological pathways for the FTO obesity risk locus, and shown that this framework generalizes to other genetic risk loci. In this presentation, I will introduce our novel V2F strategy – polygenic risk scores to function (PRS2F) – which aims to accelerate and scale the discovery of genetically anchored disease biology. Our PRS2F approach leverages our population-scale cellular biobank CellGenBank combined with genome-wide metabolic disease scores and high-dimensional imaging technologies to inform cellular programs that underlie type 2 diabetes and obesity-related disease.

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Prof. Timo Otonkoski, M.D., Ph.D.

University of Helsinki

Invited talk

What can we learn from stem cell derived islets?

Thursday 18th April 14:15

Timo Otonkoski was trained as a Pediatric Endocrinologist at the Children's Hospital in Helsinki. His main clinical specialties are childhood diabetes and hypoglycemia. His research has focused on the growth and development of the pancreatic islets. He has also made important contributions in the field of congenital hyperinsulinism and monogenic diabetes. His group has developed novel approaches for the pancreatic differentiation of human pluripotent stem cells into functional stem-cell derived islets. Combined with genome editing, this approach has been used to elucidate the mechanisms behind different types of beta-cell dysfunction, ranging from developmental defects to insulin secretory defects. The Otonkoski group belongs to the Centre of Excellence in Stem Cell Metabolism of the Research Council of Finland. Dr. Otonkoski received the Finnish physician/scientist Äyräpää Price in 2018, and the Albert Renold Prize of the EASD in 2019 for outstanding achievements in research on the islets of Langerhans.

Differentiation of human pluripotent stem cells to functional stem cell derived pancreatic islets (SC-islets) has recently become possible. This approach offers many advantages over other model systems: 1) it is based on human cells; 2) the stem cells can be derived from any individual with a desired genotype; 3) the stem cells can be efficiently genome edited; 4) the system allows modelling of all developmental stages from organogenesis to mature beta-cell function; 5) the SC-islets can be transplanted, enabling studies in humanized mice. In my lecture I will describe how this approach can be used to reveal the molecular mechanisms behind a range of phenotypes from neonatal diabetes to T2D susceptibility.

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Tom Staniford LLB (Euro) MSc CMktr FCIM FRSA GMBPsS MABP MCIPR

Invited talk

Thursday 18th April 19:00

Tom is a marketing consultant, Chartered Marketer, and Fellow of the Chartered Institute of Marketing, with Master's Degrees in Law and Psychology. Alongside marketing consultancy, he is an Associate Lecturer at the University of Exeter Business School, and speaks internationally on DEI, Rare Disease, diagnostic journeys, and patient engagement at business and healthcare organisations, conferences, and Universities.
He is a Fellow of the Royal Society for the Arts and a member of the British Psychological Society, the Association for Business Psychology, and the Chartered Institute of Public Relations. He is Vice Chair of Wheels for Wellbeing, the leading disability cycling and transport charity, Honorary Secretary of The Devon and Exeter Institution, and an advisor for the world-leading UCL Centre for Inclusive Education.

Tom is one of 16 people worldwide with MDP Syndrome, a genetic condition diagnosed in Exeter in 2013 by a number of this conference's Organising Committee. Symptoms include Type 2 Diabetes, hearing loss, lipodystrophy, and ligament contractures.
In a past life, Tom was the youngest ever British National Para-Cycling Champion and raced for GB for a number of years. He currently has far too many time-consuming interests, in cycling, IP Law, cyberpsychology, coffee, existential philosophy, and classical guitar. He is blind as a bat, deaf as a post, and not great at walking. He also likes Twitter @tomstaniford.

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Prof. Caroline Wright

University of Exeter

Invited talk

Finding new diagnoses in the Deciphering Developmental Disorders Study

Friday 19th April 9:00

Caroline Wright is a Professor of Genomic Medicine at the University of Exeter UK, Academic Director of the Rare and Inherited Disease NHS Genomic Network of Excellence, and a long-term member of the UK Deciphering Developmental Disorders Study management committee. Her main research interests are in the clinical application of genome-wide assays for the diagnosis of rare diseases, and she has expertise in analysing exome/genome sequence data particularly in rare paediatric disorders. She has funding from the Wellcome and MRC to find novel genetic causes of disease, improve the interpretation of rare genetic variants, understand the penetrance of rare pathogenic variants, and explore the policy and ethical issues associated with implementation of genome-wide sequencing in healthcare. She previously worked at the Wellcome Sanger Institute and the PHG Foundation, and trained in Natural Sciences at the University of Cambridge UK.

The Deciphering Developmental Disorders (DDD) Study (www.ddduk.org) is a translational genomics project involving >13,500 families across the UK and Ireland that aims to understand the genetic causes of severe developmental disorders using family-based exome sequencing and microarrays. More than a decade since recruitment began, we continue to return likely diagnostic variants via DECIPHER (https://www.deciphergenomics.org/), and >5,000 families have now received a precise molecular diagnosis for their condition, spanning >800 single gene disorders. We have also performed multiple burden analyses of de novo and inherited variants to discover >60 novel disorders, and investigated the contribution of mosaicism and incomplete penetrance. Through its genomic analysis of a large cohort using a hybrid clinical-research model, the DDD Study shows how the fusion of clinical expertise, genomic science, and bioinformatics can drive diagnosis and discovery in rare disease.

SGGD
9th Meeting of the Study Group on Genetics of Diabetes
EXETER 17-19TH APRIL 2024

Dr. Robert Scott

GSK

Invited talk

Genetics and Genomics in Drug Discovery and Development

Friday 19th April 9:30

Robert Scott is Vice President and Head of the Human Genetics and Genomics department at GSK. His team uses human genetic and genomic insights to identify therapeutic targets with the highest potential and to guide their development into transformative medicines for patients. This work is done in partnership across GSK and through a range of industrial and academic partnerships, including with UK Biobank, Our Future Health, 23andMe, The Broad Institute and Universities of Oxford and Cambridge.

Robert is a member of the UK National Genomics Board, a member of the UK Life Sciences Council Health Data Industry Group, and a Founding Industry Member and Scientific Advisory Board member of the Our Future Health study.

Robert joined GSK in 2016 from the Medical Research Council Epidemiology Unit, University of Cambridge. Robert was awarded an MRC Career Development Fellowship at the University of Cambridge in 2009, and progressed to lead a number of large-scale international collaborative efforts studying the aetiology and sequelae of cardiometabolic disease in the years that followed. He has published over 100 peer-reviewed articles in a range of leading journals.

In 2015, GSK scientists published the first insights describing and quantifying the role of human genetic evidence in the approval of new drugs, suggesting that targets with human genetic support were around twice as likely to be approved as those without. In the last decade, there has been an explosion of genetic and genomic data, and an increasing focus on the use of these data and insights across the industry. I will describe the rationale for use of genetic insights in drug discovery and development, and how genetic and genomic evidence are developed and deployed at GSK, including some recent examples. I will also seek to review the limitations and challenges we face in the development and application of genetic evidence, and some future opportunities to improve our impact on drug discovery and development.

SGGD
9th Meeting of the Study Group on Genetics of Diabetes
EXETER 17-19TH APRIL 2024

Prof. Jonathan Mill

University of Exeter

Invited talk

Epigenetic and transcriptional pathways to brain disease

Friday 19th April 10:00

Jonathan Mill is Co-Head of Department for the Clinical and Biomedical Sciences in the Medical School and Professor of Epigenomics at the University of Exeter Medical School where he heads the Complex Disease Epigenomics Group. He graduated with a degree in Human Sciences from Oxford University, where he took a particular interest in cannibalism, before undertaking his PhD in psychiatric genetics at King's College London. He joined Exeter in 2012, establishing a group studying the factors controlling transcriptional regulation in the central nervous system, with a focus on the role of epigenomic variation in disorders of the brain including schizophrenia, depression, Alzheimer's disease and other types of dementia.

There are many parallels between diabetes and disorders of the human central nervous system, including neurodevelopmental and neurodegenerative phenotypes. In this talk I will describe our efforts to study the causes and consequences of molecular variation in the cortex, and the role this plays in disorders including autism, schizophrenia, Alzheimer's disease and other forms of dementia. Despite major advances in understanding the risk factors (both genetic and environmental) for these diseases, the mechanisms involved in the onset and progression of pathology are not fully understood and long-term treatments to reverse cellular disease processes in the brain remain elusive. Our work aims to characterise the regulatory regions, epigenetic modifications and transcriptional patterns defining the different brain regions and cell-types in the human central nervous system, and assess their role in neurodevelopment, ageing and disease. I will describe the dynamic nature of DNA modifications across human brain development and ageing, and describe the impact of genetic variation on the epigenome during the life-course. I will outline how we are using novel long-read sequencing approaches to characterise full-length transcripts in the brain, identifying evidence considerable isoform diversity in the human cortex and a role for alternative splicing in multiple brain disorders. Finally, I will show how these approaches can be used to explore mechanistic pathways in diabetes via the profiling of human pancreas tissue and regions of the brain involved in the regulation of metabolis

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Prof. Ewan Pearson

University of Dundee

Invited talk

Precision medicine in diabetes

Friday 19th April 11:00

Ewan Pearson is Professor of Diabetic Medicine at the University of Dundee, Visiting Professor at the University of Edinburgh, and Honorary Consultant in Diabetes and Endocrinology at Ninewells Hospital and Medical School in Dundee. He has recently been appointed as an associate director of the British Heart Foundation Data Science Centre, where he leads the Diabetes Data Catalyst. Ewan has been awarded the Royal College of Physicians of Edinburgh Croom Lecture, the Diabetes UK RD Lawrence Lecture and Dorothy Hodgkin Lecture, and the EASD Minkowski Award. He was recently elected to be a Fellow of the Royal Society of Edinburgh.

Ewan's research interests have been in the phenotypic and genotypic determinants of drug response in diabetes, and in stratified approaches to the management of diabetes. Ewan's earlier work established that patients with monogenic diabetes did not need insulin treatment (Lancet 2003, NEJM 2006), paving the way for 1000s of patients to transition off long term insulin treatment onto oral medication. Ewan has recently been awarded £2.8M from the Chief Scientists Office to implement precision diabetes care within NHS Tayside.

This talk will discuss advances in precision medicine and pharmacogenetics in diabetes. I will highlight recent work on how phenotypic variation matters, and how this maps to genetic variation, and will provide an overview of how genetic variants alter glycaemic response to commonly used diabetes drugs and how these inform on disease and drug mechanism. I will finish with an overview of iDiabetes – an intelligent diabetes platform that we will be using to implement precision diabetes care in Tayside in 2024.

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Dr. Miriam S. Udler, MD, PhD

Massachusetts General Hospital, Harvard Medical School, Broad Institute of MIT and Harvard

Invited talk

Are genetic diabetes clusters ready for the clinic?

Friday 19th April 11:30

Miriam S. Udler, M.D, Ph.D. is a practicing endocrinologist at Massachusetts General Hospital (MGH) and an Assistant Professor at Harvard Medical School. Dr. Udler is the founding director of the MGH Diabetes Genetics Clinic, which provides genetic testing, counseling, and management to patients with monogenic forms of diabetes. She is also an Associate Member of the Broad Institute of MIT and Harvard. Her research team focuses on genetic contribution to diabetes risk and clinical applications of genomic data, including using genetics to identify atypical forms of diabetes and to dissect disease heterogeneity.

The vast discovery of genetic contribution to type 2 diabetes offers an important opportunity to gain insight into disease mechanisms and potentially identify disease endotypes. Dr. Udler and her team have developed approaches to perform physiologically informed clustering of disease genetic variation. These genetic clusters can be used to generate process-specific polygenic scores, which inform on disease heterogeneity as well as cellular and molecular phenotypes. Dr. Udler will describe current progress in the development of type 2 diabetes genetic clusters and process-specific polygenic scores, with a focus on potential clinical applications.

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Amélie Bonnefond PhD

INSERM

Invited talk

The impact of rare variants in common diabetes and obesity towards precision medicine

Friday 19th April 12:00

Amélie Bonnefond graduated with a PhD from University of Lille in 2010. Her scientific career has been focused on the dissection of the genetic etiologies of type 2 diabetes and obesity in order to elucidate their pathophysiology towards a better stratification of the patients and a putative identification of new drug targets. She is Research Director at the INSERM/CNRS 1283/8199 unit and heads a team tackling genetics and genomics of type 2 diabetes and obesity. She is the current scientific director of the LIGAN-PM platform dedicated to the use of next-generation sequencing in precision medicine. She has published >150 peer-reviewed scientific papers. She was laureate of the 2012 Rising Star award from EASD, the 2018 Auguste Loubatières award from the French-speaking Association for Diabetes (SFD), the 2021 Minkowski award from EASD, and two European Research Council Grants (Starting in 2016 and Consolidator in 2022).

During this presentation, Amélie Bonnefond will highlight the significance of investigating rare variants in the pathophysiological advancements of type 2 diabetes and obesity. She will introduce the concept of oligogenic forms of diabetes and obesity and demonstrate how studying these forms (notably via functional genetics) can lead to new pathophysiological insights and even the discovery of novel therapeutic targets.

Oral presentations

Alicia Huerta-Chagoya

Broad Institute of Harvard and MIT

Oral presentation

Wednesday 17th April 15:30

Alicia Huerta-Chagoya[1,12], Joohuyn Kim[2], Ravi Mandla[1,12], Yingchang Lu[2], Jaehyun Park[2], Lauren Petty[2], Ken Suzuki[3], Simon Lee[4], Jaewon Choi[5], Kuang Lin[6], Hong Kiat Ng[7], Mi Yeoung Hwang[8], Hye-Mi Jang[8], Madhusmita Rout[9], Marie Loh[7], Marijana Vujkovic[10], Benjamin Voight[10], Xueling Sim[11], Michael Preuss[4], Ruth Loos[4], Jennifer Below[2], Robin Walters[5], Young Jin Kim[8], Bong-Jo Kim[8], Dharambir Sanghera[9], Sean Kwak[5], Tian Ge[12], VA Million Veteran Program, Jose C. Florez[13], Alisa Manning[1,12], Maggie Ng[2], Josep M. Mercader[1,12], Diabetes Polygenic Risk Scores in Multiple ancestries (D-PRISM).

[1] Programs in Metabolism and Medical & Population Genetics, Broad Institute of Harvard and MIT, [2] Vanderbilt Genetics Institute, Vanderbilt University Medical Center, [3] Department of Statistical Genetics, Osaka University, [4] The Charles Bronfman Institute for Personalized Medicine, Icahn School of Medicine at Mount Sinai, [5] Seoul National University Hospital, [6] Nuffield Department of Population Health, University of Oxford, [7] Nanyang Technological University, Clinical Sciences Building, Singapore, [8] Department of Precision Medicine, National Institute of Health, Republic of Korea, [9] Department of Pediatrics, Section of Genetics, University of Oklahoma, [10] Division of Translational Medicine and Human Genetics, University of Pennsylvania, [11] National University of Singapore and National University Health System, Singapore, [12] Center for Genomic Medicine, Mass General Research Institute, [13] Department of Medicine, Massachusetts General Hospital.

Polygenic risk scores for the prediction of type 2 diabetes and complications in diverse ancestries.

Introduction. Most polygenic risk scores (PRS) for type 2 diabetes (T2D) are developed based on the European population despite T2D disproportionately impacting non-Europeans, undermining their utility in the clinical setting.

Methods. We harmonized T2D genome-wide association study meta-analyses from 5 major continental ancestries (360K cases, 1.8M controls, 32% of non-European ancestry), constructed ancestry-specific and multi-ancestry PRS using PRS-CS and PRS-CSx, and evaluated their performance using the area under the receiver operating characteristic curve (AUC), the odds ratio (OR) per standard deviation (SD) change in PRS, and the discriminative capability of the tail of PRS distribution in independent datasets (54K cases, 161K controls). In the All of Us cohort, we also assessed their ability to predict macrovascular and microvascular complications.

Results. In all ancestries, the multi-ancestry PRS showed better predictive power than the ancestry-specific PRSs. For example, when using multi-ancestry PRS, individuals of Admixed American ancestry in the top 2.5% of the PRS distribution have a predicted T2D risk 7.5-fold larger than the interquartile (OR=7.5 [5.6-9.9], $p=8\times10^{-45}$) compared to the European-based PRS (OR=6.2 [4.7-8.2], $p=4\times10^{-38}$) or the Admixed American-based PRS (OR=2.3 [1.8-2.9], $p=2\times10^{-11}$). We also show that the multi-ancestry PRS is associated with a higher risk of diabetic retinopathy in African American (OR/SD=1.2 [1.1-1.4], $p=4\times10^{-5}$), Admixed American (OR/SD=1.4 [1.3-1.6], $p=2\times10^{-8}$), and European populations (OR/SD=1.3 [1.2-1.4], $p=2\times10^{-10}$).

Interpretation. We leveraged genetic data from the major continental ancestries to develop and validate the most comprehensive T2D PRS, which also showed utility in identifying patients with T2D who are at high risk of developing diabetic retinopathy in diverse ancestries.

Miriam Samuel

Queen Mary University of London

Oral presentation

Wednesday 17th April 15:45

Authors: **Miriam Samuel [1],** Benjamin M Jacobs [1,2], Daniel Stow [1], Sam Hodgson[1], Julia Zöllner [1,3], Stavroula Kanoni [4], Saeed Bidi [1], Genes & Health Research Team, Klaudia Walter [5], Claudia Langenberg [6, 7], Ruth Dobson [1,2], Caroline Morton [1], Hilary C. Martin [5], Maik Pietzner [6, 7], David A van Heel[1,8], Rohini Mathur [1], Moneeza K Siddiqui [1], Sarah Finer [1]

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8. Blizard Institute, Queen Mary University of London

A South Asian-specific missense variant in *PIEZO1* may distort relationships between HbA1c and blood glucose.

Introduction: Glycated haemoglobin (HbA1c) is used to diagnose and monitor diabetes. Genetic analyses have demonstrated that HbA1c underestimates blood glucose amongst individuals with red blood cell (RBC) conditions of Black African/Caribbean ancestry, but its accuracy in adults of South Asian ancestry (SA) has not been evaluated. We explored the genetic architecture of HbA1c to identify SA-specific variants.

Methods: We used data from Genes & Health, a longitudinal study of ~50,000 British Bangladeshi and Pakistani volunteers. We performed genome-wide association studies of HbA1c (from healthcare records, n=32,589), and multi-ancestry meta-analysis and fine mapping by combining with pan-ancestry HbA1c genetic association studies from UK-Biobank.

Results: We replicated loci previously discovered in European-centric studies (e.g. *GCK* and *TCF7L2*) and found several novel associations, including in *MTNR1B* and *IGF2BP2*. Multi-ancestry fine mapping revealed an ancestry-specific association in *PIEZO1* (with a frequency of 3.9% in SAs but ultra-rare in other ancestries) mapping to $rs563555492_T$ (Leu2277Met), which was also associated with RBC traits but not blood glucose. Carriers of the $rs563555492_T$ allele had lower HbA1c values (6mmol/mol difference between homozygous groups), likely via its effect on RBCs and not glucose homeostasis. They also experienced delayed diabetes diagnosis.

Conclusion: We report a novel SA-specific variant associated with reduced HbA1c and altered RBC traits, but not associated with blood glucose. Underestimation of glycaemia by HbA1c could delay diabetes diagnosis and treatment, and contribute to diabetes inequalities. Increased diversity in genetic analyses is vital to ensure clinically-relevant ancestry-specific variants are identified.

Gareth Hawkes

University of Exeter

Oral presentation

Wednesday 17th April 16:00

Identifying rare non-coding regulatory regions for HbA1c using Whole Genome Sequences

G. Hawkes[1], R.N. Beaumont[1], A.R. Wood[1], K. A. Patel[1], A. Murray[1], L. M. Jackson[1], I. Barroso[1], C. F. Wright[1], T. M. Frayling[1,2], A. K. Manning[3], M. N. Weedon[1]

[1] Clinical and Biomedical Sciences, Faculty of Health and Life Sciences, University of Exeter, Exeter, UK
[2] Faculty of Medicine, Department of Genetic Medicine and Development, CMU, Geneva, Switzerland
[3] Broad Institute, Boston, USA

Most sequence-based association studies for common human phenotypes have focussed on common variants, and rare variants that reside in the coding regions of the genome. However, the recent release of whole-genome-sequence (WGS) data in 500,000 individuals in the UK Biobank, provides an unprecedented opportunity to examine rare, non-coding variants and their contribution towards the genetic architecture of common traits.

We performed a WGS analysis for glycated haemoglobin (HbA1c) in 427,586 individuals from UK Biobank to identify novel rare (<0.1% minor allele frequency, MAF) non-coding genetic associations, and replicated our results in 48,169 individuals of European ancestry in All of Us with measured HbA1c. We classified variants into coding, proximal-regulatory and intergenic-regulatory, and further stratified by measures of conservation, constraint and deleteriousness.

We identified 17 rare non-coding variant aggregates after adjusting for common genetic variation (>0.1% MAF), 5 of which would not have been identified by single variants alone. Our results implicate long non-coding RNA, and regulation of genes involved in glycolysis, blood-cell turnover and glucose uptake. We also identified 16 rare non-coding single variants, with effects sizes ranging from -2.28 mmol/mol [-2.37, -2.20, *P* = 1.47e-14], a constrained regulatory variant proximal to *ZC3H18*, to 1.97mmol/mol [1.92, 2.02, *P* = 1.04e-26], an intronic variant in *LUC7L*. In the small (11% discovery sample size) replication dataset, 15/16 were directionally consistent, and 6/16 replicated at P<0.05, consistent with our findings being true positives.

Our findings demonstrate the importance for rare non-coding variant discovery for glycaemic traits, which may lead to novel gene targets.

Robin Beaumont

University of Exeter

Oral presentation

Wednesday 17th April 16:15

Rare variant associations with birth weight highlight genetic links with later metabolic health

Robin N. Beaumont[1],Katherine A. Kentistou[2], Brandon E. M. Lim[1], Lena R. Kaisinger[2], Luke Sharp[1], Kashyap A. Patel[1], Gareth Hawkes[1], Eugene J. Gardner[2], Andrew R. Wood[1], Yajie Zhao[2], Felix R. Day[2], Ken K. Ong[2,3], Rachel M. Freathy[1], John R. B. Perry[2,4]

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Lower birth weight (BW) is associated with later Type 2 Diabetes (T2D) risk. Genome-wide association studies of birth weight have identified common variants in >240 genomic regions, including several T2D loci. However, causal genes remain mostly unknown. Rare variant associations may highlight genes linking BW with later metabolic health, but to date few rare variants are known to influence BW.

We annotated rare (minor allele frequency <0.1%) protein-truncating or high-impact missense variants in whole exome sequence data in UKBiobank for up to 252,329 participants with self-reported own BW (fetal variants), and 195,653 mothers who reported BW of first child (maternal variants). Variants within each gene were collapsed to perform gene burden tests.

We identified 11 genes with rare fetal variant BW effects ($P<1.5x10^{-6}$), of which 2 also showed maternal effects ($P<1.6x10^{-6}$). One additional gene (*ADAMTS8*) showed maternal effects only. We observed directionally consistent associations in an independent sample (n=45,622; sign text P=0.01). Of the associated genes, *IGF1R, PAPPA* and *PAPPA2* have roles in insulin-like growth factor (IGF) bioavailability and signalling. *PPARG, INHBE* and *ACVR1C* are involved in adipose tissue regulation, while *PPARG* is also implicated in placental angiogenesis. Rare BW-raising variants *INHBE* and *ACVR1C* also showed favourable adiposity associations in adults, while rare BW-lowering variants in *IGF1R* increase T2D risk. Other identified genes were *NOS3*, *NRK*, *ADAMTS8*, *HGS*, *ZBTB10*, and *MED7*.

Analysis of rare coding variants identified key regulators of IGF bioavailability and signalling, fetal adipose tissue and fetoplacental angiogenesis as determinants of BW, with relevance to long-term metabolic health.

Ailsa MacCalman

University of Exeter

Oral presentation

Thursday 18th April 14:45

Ultra-deep targeted transcriptome sequencing identifies isoform diversity across human pancreatic development

Ailsa MacCalman, Elisa De Franco, Szi Kay Leung, Rosie Bamford, Aaron Jeffries, Nick Owens, Jonathan Mill.

Introduction-

Understanding transcriptional isoform diversity during human pancreas development can shed new light on gene regulation and aid the interpretation of apparently non-coding variants in individuals with monogenic diabetes. Our current understanding of this diversity is limited due to scarcity of fetal tissue. In this study, we used targeted long-read RNA sequencing to characterise isoform abundance and diversity resulting from alternative splicing events across human pancreatic development.

Methods-

We performed targeted long-read RNA sequencing using Oxford Nanopore Technologies on 31 human fetal pancreatic samples spanning 6 – 21 post conception weeks. We targeted 45 genes, including aetiological genes for monogenic diabetes and congenital hyperinsulinism, as well as genes critical for pancreas development and function.

Results-

We detected extensive isoform diversity in the 45 target genes, with the identification of >900 novel transcripts. Long-read sequencing enabled the identification of multiple alternative splicing events (e.g. exon skipping). Of note, we identified > 600 novel exons within the transcripts of the 45 genes of interest. Seven genes were characterized by dramatic changes in major isoform usage across pancreas development (*CNOT1*, *PAX6*, *STAT3*, *GATA4*, *FICD*, *NEUROG3*, *ZBTB20*). For instance, *PAX6* was found to have 33 differentially expressed transcripts, with > 18% being identified as novel.

Interpretation-

We find widespread evidence of AS events including the presence of novel exons, which have potential clinical relevance in identifying novel causes of disease. We confirm the importance of AS in the human pancreas in dramatically increasing transcriptional diversity, representing an important mechanism underpinning gene regulation across development.

Amna Abdel Khamis

University of Lille

Oral presentation

Thursday 18th April 15:00

Age-related DNA methylation dynamics in insulin-sensitive tissues and their implications in metabolic health and obesity

Amna Khamis[1,2,3], Mathilde Boissel[1,2], Lijiao Ning[1,2], Lucas Maurin[1,2], Mehdi Derhourhi[1,2], Violeta Raverdy[2,5], Bart Staels[2,4], Philippe Lefebvre[2,4], François Pattou[2,5], Amélie Bonnefond[1,2,3], Philippe Froguel[1,2,3].

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[5]Inserm, Translational Research in Diabetes (U1190), Lille, France.

Introduction:
Epigenetics and transcriptomics in metabolic tissues could unveil mechanisms in obesity and age-related complications.

Methods:
We analysed DNA methylation in 84 muscle and 110 liver of individuals with severe obesity. We performed an epigenome wide association study (EWAS) for age. We generated transcriptomics and genotyping data, and developed a pipeline to identify age-associated CpG target genes, while taking into account genetic confounding factors.

Results:
Our EWAS revealed 303 CpGs in muscle and 1,258 CpGs in liver associated with age, with only 33 shared between them. These CpGs were associated with the cis-gene expression of only 46 and 83 muscle and liver genes, respectively. The majority (87%) did not implicate the nearest gene. Our multi-omics approach outperformed standard transcriptome-wide association in identifying robust genes within both tissues. Several target genes were involved in muscle and liver function, and/or sarcopenia or metabolic dysfunction-associated steatohepatitis (MASH). Glucose metabolism was the only shared pathway between the two tissues. Most liver genes were positively associated with late postprandial c-peptide (120 min, an index of insulin resistance), cholesterol and liver inflammation. In muscle, several genes were negatively associated with early postprandial c-peptide (30 min, index of insulin secretion), such as *TPI1,* which increased with age and c-peptide. Following bariatric surgery, *TPI1* expression was associated with decreased HbA1c, suggesting a role in glucose tolerance and weight loss following bariatric surgery.

Interpretation:
Our findings highlight the significant consequences of age-related DNA methylation changes in insulin-sensitive tissues, directly linked to clinical variation in obesity and its surgical treatment.

Ozvan Bocher

Institute of Translational Genomics, Helmholtz Zentrum München

Oral presentation

Thursday 18th April 15:15

Unravelling the interplay between type 2 diabetes, genetics and metabolite levels

Ozvan Bocher[1], Archit Singh[1,2,3], Ana Luiza Arruda[1,2,3], Ene Reimann[4], Urmo Võsa[4], Andrei Barysenka[1,5], William Rayner[1,5], Reedik Mägi[4], Eleftheria Zeggini[1,5]

1. Institute of Translational Genomics, Helmholtz Zentrum München, German Research Center for Environmental Health, Neuherberg, Germany
2. Technical University of Munich (TUM), TUM School of Medicine, Munich, Germany
3. Helmholtz Association - Munich School for Data Science (MUDS)
4. Estonian Genome Center, Institute of Genomics, University of Tartu, Tartu, Estonia
5. Technical University of Munich (TUM) and Klinikum Rechts der Isar, TUM School of Medicine, Munich, Germany

Numerous metabolite levels have been associated with the occurrence of type 2 diabetes (T2D), but their causal role in T2D development and the involvment of genetics in mediating those relationships remain to be elucidated. We sought to investigate the interplay between genetics, metabolomics and T2D risk in the UK Biobank cohort by using bidirectional two-sample Mendelian Randomization (MR) and interaction QTL analyses. In the forward MR, we describe 63 metabolites with a causal effect on T2D, including glucose, apolipoprotein B and various lipid classes. In the reverse direction, we report a causal effect of T2D liability on 178 metabolite levels (with p-values down to 10^{-175}), including an increase in alanine, valine and glucose levels, and a decrease in levels from cholesterol classes. Secondly, we describe 14 metabolites which exhibit a different genetic regulation between T2D cases and controls. Four of these metabolites, L_VLDL_FC_pct, L_VLDL_TG_pct, L_LDL_PL_pct and S_HDL_FC_pct, were replicated in the Estonian Biobank with p-values down to 9.88×10^{-13} and 8.1×10^{-4} in the discovery and replication cohort respectively. These variants reside in two different genomic regions and are significant QTLs for the corresponding metabolites in healthy individuals but not in individuals with T2D. Additionally, these variants are not associated with T2D, suggesting that the different genetic regulation at these loci is a consequence rather than a cause of T2D development. This work provides a better understanding of the metabolic changes induced by the occurrence of T2D and provide potential directions to investigate T2D consequences and subsequent complications.

Ann Madsen

Steno Diabetes Center Aarhus

Oral presentation

Thursday 18th April 15:30

Genetic architecture of oral glucose-stimulated insulin release provides biological insights into type 2 diabetes aetiology

A L Madsen[1*], S Bonàs-Guarch[2,3,4*], S Gheibi[5], R Prasad[6], J Vangipurapu[7], V Ahuja[19], LR Cataldo[1,5], O Dwivedi[19], G Hatem[6], G Atla[2,3,4], M Guindo-Martínez[1], A M Jørgensen[1], A E Jonsson[1], I Miguel-Escalada[2,3,4], A Linneberg[8,7], Tarunveer S. Ahluwalia[10,11], T Drivsholm[8,12], O Pedersen[1], T I A Sørensen[1,13], A Astrup[14], D Witte[15], P Damm[16], T D Clausen[17], E Mathiesen[16], T Pers[1], R J F Loos[1], L Hakaste[18,19], M Fex[5], N Grarup[1], T Tuomi[6,18,19,20], M Laakso[7], H Mulder[5], J Ferrer[2,3,4†], T Hansen[1†]. *Shared first author, †Contributed equally

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Introduction

The function of β-cells in response to glucose is crucial in the development of type 2 diabetes (T2D). Understanding this insulin secretory function could benefit the health of β-cell. This study aims to investigate the polygenic architecture of β-cell function and its implications for T2D development.

Methods

Genetic variants associated with eight different indices of the glucose-stimulated insulin secretory function was identified using data from approximately 26,000 individuals of European ancestry. These variants were then examined in relation to other traits relevant for diabetes. Subsequently, we integrated human islet transcriptomic and epigenomic data with the genetic association findings to identify their candidate target molecular effectors. Finally, we selected two candidate genes for silencing and assessed their influence on glucose-stimulated insulin release using a human (EndoC-βH1) and rat (INS-1 832/13) β-cell lines.

Results

Our analyses revealed 55 independent genetic association with β-cell function at 44 loci, of which 14 were novel. We also found that these genetic variants exert their influence on T2D risk through diverse molecular mechanisms. Integration of genetic association results with human islet transcriptomic and epigenomic data led to the identification of 31 novel candidate molecular mediators of insulin release. Finally, we validated that two candidate target genes influence glucose-stimulated insulin release using an *in vitro* cell model.

Interpretation

Overall, this research expand our understanding of the polygenetic architecture of glucose-responsive insulin release and has identified potential regulators of β-cell function, providing valuable insights for future strategies aimed at improving β-cell health.

Sadia Saeed

University of Lille

Oral presentation

Thursday 18th April 16:15

Homozygous mutations in SREK1 linked to a new condition of syndromic obesity

Sadia Saeed1,2,3 , Anna-Maria Siegert4 , Loraine Tung4 , Roohia Khanam5 , Qasim M Janjua6 , Jaida Manzoor7 , Brian Y. H. Lam4 , Sherine Awad4 , Bénédicte Toussaint2,3, Emmanuel Vaillant2,3, Souhila Amanzougarene2,3, Mehdi Derhourhi2,3 , Stephen O'Rahilly4 , Anthony P. Goldstone8 , Amélie Bonnefond1,2,3 , Muhammad Arslan5 , Giles S.H. Yeo4 , and Philippe Froguel1,2,3 1

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Introduction: Mendelian forms of obesity have revealed brain circuits that play a crucial role in regulating appetite. Research on the Severe Obesity in Pakistani Population (SOPP) cohort, consisting of consanguineous families, has expanded this knowledge by identifying novel genes like ADCY3 and P4HTM, linked to severe obesity and related abnormalities.

Methods: We employed a gene-centric analysis using MiST method on exome data from SOPP (n=492) and >1000 subjects from general population to identify genes with potentially deleterious homozygous variants in the cases. We conducted functional analyses on iPSCderived hypothalamic neurons, complemented by RNA sequencing. Subsequently, targeted clinical re-examinations were performed.

Results: MiST analysis revealed three homozygous missense mutations in SREK1 across three unrelated individuals presenting with hyperphagic obesity and neurodevelopmental delay. This gene encodes a glutamic acid and lysine-rich protein that plays a role in RNA splicing. These mutations comprise two variants located in the N-terminus RNA recognition domains (P95L, T194M) and one within the C-terminus (E601K). SREK1 is expressed throughout the hypothalamus and structural predictions suggested these mutations adversely affect RNA-binding capabilities. Functional assays on iPSC-derived hypothalamic neurons revealed that these SREK1 variants precipitate the downregulation of SNORD115 and SNORD116, with the latter known to cause hyperphagia and weight gain in Prader-Willi Syndrome (PWS). Clinical reassessment of the patients identified several phenotypic characteristics consistent with PWS, further supporting our genetic and functional findings. Interpretation: We identified a novel form of syndromic obesity due to recessive mutations in SREK1 associated with clinical and molecular disturbances paralleling those seen in PWS.

Thomas Laver

University of Exeter

Oral presentation

Thursday 18th April 16:30

Disease-causing low-level mosaic variants can be detected in blood samples from individuals with hyperinsulinism

Thomas W Laver[1], Matthew N Wakeling[1], Jasmin J Hopkins[1], Benjamin Spurrier[1], Sabrina Wright[1], Nina Smaller[1], Sam Salisbury[1], Anna-Marie Johnson[12], Jayne AL Houghton[2], Matthew B Johnson[1], Sarah E Flanagan[1]

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[2]Exeter Genomics Laboratory, Royal Devon University Healthcare NHS Foundation Trust, Exeter, UK.

Introduction

Mosaic variants occur post-zygotically and are not present in all tissues. They may not be detected in samples available for genetic testing if only present at a low-level; standard analysis methods cannot reliably call variants <8% in targeted next-generation sequencing (tNGS). Hyperinsulinism is the most common cause of severe, persistent hypoglycemia in infancy. ~50% of patients with hyperinsulinism do not have a genetic diagnosis. Previous studies identified pathogenic variants in pancreas samples from individuals with hyperinsulinism that were not detected in the blood. We hypothesised that some undiagnosed patients may have mosaic variants in the pancreas that are at low-levels in blood-derived DNA.

Methods

We screened 1550 patients with hyperinsulinism for low-level variants in the known causative genes. We used specialized low-level variant calling software (Mutect2) to reanalyse routinely collected tNGS data. We then sought to confirm these variants using digital droplet PCR (ddPCR) and high-depth unique-molecular-identifier sequencing (UMI-seq).

Results

Screening of tNGS data identified putative low-level mosaic causative variants in 55 individuals. Our initial testing of 36 of these variants by ddPCR/UMI-seq confirmed 8 true disease-causing variants (2 *GCK*, 6 *GLUD1*) at 1.3-5.7% in the blood of children with hyperinsulinism. The remaining 28 tested were false positives in the tNGS.

Interpretation

Low-level mosaic variants are an important cause of hyperinsulinism, currently missed by standard genetic testing. Incorporating screening for low-level mosaic variants into genetic testing pipelines would improve diagnostic yield but currently requires orthogonal testing to confirm variants. Our findings may be important for other organ-specific monogenic disorders.

Endrina Mujica

Uppsala University, Sweden

Oral presentation

Thursday 18th April 16:45

From 58 type-2 diabetes candidate genes to 5: A validated 2-step *in vivo* prioritization system

Endrina Mujica[1], Anastasia Emmanouilidou[1], Hanqing Zhang[1], Eugenia Mazzaferro[1], Christoph Metzendorf[1], Manoj Bandaru[1], Naomi Cook[1], Joao Costa[1], Ghazal Alavioon[1], Klaus Stensgaard Frederiksen[2], Djordje Djordjevic[2], Sara Gry Vienberg[2], Anders Larsson[3], Jason Flannick[4], Amin Allalou[5], Marcel den Hoed[1]

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INTRODUCTION: GWAS identified hundreds of type-2 diabetes (T2D)-associated loci. We functionally characterize 58 T2D candidate genes and prioritize five novel culprits.

METHODS: We characterized human genes one-by-one, by jointly targeting their zebrafish orthologues using CRISPR/Cas9, in single cell fertilized eggs that transgenically express fluorescent labels on beta cell nuclei (Tg[-1.2*ins*:H2B-mCherry]) and hepatocytes; (Tg:*fabp10a*:EGFP). Larvae were overfed from day 5 to 10, before acquiring optical sections of pancreatic islets and liver using semi-automated fluorescence microscopy. Liver fat (trait 1); beta cell number (2); and average (3) and total (4) insulin expression were quantified using deep learning-based neural networks. After imaging, larvae were sacrificed and homogenized for enzymatic assessment of glucose content (5). DNA was isolated for PCR-based fragment length analyses at CRISPR-targeted sites, to ascertain mutagenesis (n_{total}=6604).

RESULTS: For 13 of 13 established diabetes genes, mutations affect ≥1 T2D trait in overfed larvae. Moreover, 10 of 35 candidate genes without functional evidence of a role in T2D (in 2019) affect ≥1 T2D trait. Genes affecting ≥1 T2D trait in zebrafish larvae are enriched for common (P=7.9E-3) and rare (P=2.7E-3) variant associations with T2D in humans. For the10 previously uncharacterized genes, we next assessed effects on basal glucose content in CRISPR-edited, unfed, 7-day-old larvae. Of these, *poldip2, znf598, atp2a3, tp53inp1* and *sirt1* affect basal glucose regulation in zebrafish.

INTERPRETATION: Systematically characterizing candidate genes for a role in T2D traits in zebrafish larvae can prioritize putative causal genes for further in-depth characterization, and improve our understanding of disease etiology in humans.

Word count: 248

KEY WORDS: *CRISPR/Cas9, zebrafish larvae, deep learning, automated fluorescence microscopy, common and rare variants.*

Yue Tong

University of Brussels

Oral presentation

Thursday 18th April 17:00

Homozygous and Heterozygous INS Mutations Cause Divergent Clinical and iPSC-Derived β-Cell Phenotypes

Authors and affiliations
Yue Tong[1], Marianne Becker[2], Ulrike Schierloh[2], Ying Cai[1], Flávia Natividade da Silva[1], Leena Haataja[3], Federica Fantuzzi[1], Toshiaki Sawatani[1], Chiara Vinci[1], Maria Lytrivi[1], Nathalie Pachera[1], Peter Arvan[3], Carine De Beaufort[2], Miriam Cnop[1];
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Introduction
The heterozygous c.16C>T (p.Arg6Cys, INSR6C) *INS* mutation has been described to cause monogenic diabetes, but its pathogenicity has recently been questioned. INSR6C preproinsulin exhibits impaired translocation into the endoplasmic reticulum, potentially affecting insulin secretion. We discovered a family with homozygous and heterozygous INSR6C mutations and examined pathogenic mechanisms using induced pluripotent stem cell (iPSC) models.
Methods
We reprogrammed mononuclear cells from 2 patients into iPSCs, CRISPR/Cas9-corrected the mutations and differentiated iPSCs into pancreatic β-cells.
Results
A homozygous INSR6C mutation was detected in a girl who developed diabetes at 11 years with HbA1c 11.9%, plasma C-peptide 3.3 ng/ml, glycemia 286 mg/dl, no ketoacidosis nor β-cell autoantibodies. On hybrid closed loop HbA1c remained >8%. Two homozygous INSR6C uncles developed diabetes at 9 and 20 and were insulin-treated. Her heterozygous father developed diabetes at 32, and mother impaired glucose tolerance at 41. We differentiated the proband's and father's iPSCs into INSR6C β-cells. Western blots showed 5.3- and 2.0-fold higher preproinsulin-to-proinsulin ratio in homozygous and heterozygous INSR6C β-cells, respectively, compared with corrected cells. Homozygous β-cells showed 2.9- and 4.0-fold lower proinsulin and insulin contents, respectively, while heterozygous cells had normal levels. Glucose-stimulated insulin secretion was 2.7- and 2.4-fold lower in homozygous and heterozygous β-cells, respectively; forskolin-stimulated secretion was impaired in homozygous cells only.
Interpretation
The homozygous INSR6C mutation causes β-cell preproinsulin accumulation, reduces proinsulin and insulin content and impairs insulin secretion, triggering early-onset insulin-dependent diabetes. The heterozygous INSR6C causes a much milder β-cell phenotype, consistent with accumulating genetic evidence suggesting lack of pathogenicity.

Highly commended posters

Daniel Rosoff

University of Oxford

Highly commended poster No: 1

Multi-ancestry Mendelian randomization study investigating relationships of PCSK9 and HMGCR inhibition with type 2 diabetes

Daniel B. Rosoff[1,2,3], AB, ScB; Josephin Wagner[1], MD, MS; Lauren Park[1], BS; Ali Hamandi[1], BS; Natalie Ellis[1], BS; Tyler Perlstein[1], BS; Jeesun Jung[1], PhD; Pal Pacher, MD, PhD[4]; Constantinos Christodoulides[2], MBChB, MRCP, PhD; George Davey Smith[3], MD, DSc; David Ray[2,5], FRCP, PhD; Falk W. Lohoff[1#], MD

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ABSTRACT

Introduction: The prevalence of type 2 diabetes (T2D) varies between across different ancestries and is highly comorbid with coronary artery disease (CAD). However, the impact of genetically-proxied proprotein convertase subtilisin/kexin 9 (PCSK9) and HMG-CoA Reductase (HMGCR) inhibition on T2D in non-European cohorts remains unknown.

Methods: We used genetic variants in the *PCSK9* and *HMGCR* loci from genome-wide association studies (GWAS) summary-level data of low-density LDL-C in five ancestral cohorts (East Asian (EAS), South Asian (SAS), Hispanic (HISP), African (AFR), and European (EUR)) and performed drug-target Mendelian randomization (MR) evaluating the impact of PCSK9 and HMGCR inhibition on T2D risk and glycemic traits.

Results: MR estimates suggested null relationships of genetically-proxied PCSK9 inhibition on T2D risk among EAS, SAS, HISP, and EUR cohorts. PCSK9 inhibition in AFR increased T2D (odds ratio [OR]=1.53, [1.058, 2.22], P-value=0.024). Analyses with instruments constructed using circulating PCSK9 protein levels and liver and pancreas *PCSK9* expression were also null, suggesting limited glycemic associations with lowered PCSK9 protein levels and gene expression in therapeutically relevant tissues. Genetically-proxied HMGCR inhibition increased risk for T2D in EAS (OR=1.44 [1.30, 1.61], P-value=9.8×10^{-12}) and EUR ancestries (OR=1.52 [1.21, 1.90], P-value=3.3×10^{-4}). MR estimates from complementary methods and alternate drug-target instruments aligned with the primary results, strengthening causal inference.

Interpretation: Ancestry-specific analyses suggest generally neutral relationship of long-term genetically-proxied PCSK9 inhibition with T2D. Conversely, genetically-proxied HMGCR inhibition increased T2D risk in EAS and EUR cohorts, which together informs our understanding of the long-term glycemic profiles for PCKS9 and HMGCR inhibition in diverse populations.

Jan-Inge Bjune

University of Bergen

Highly commended poster No: 2

Irx3 controls a sumoylation-dependent epigenetic switch between adipogenesis and osteogenesis

Jan-Inge Bjune[1,2,3], Samantha Laber[4], Laurence Lawrence-Archer[1,3], Xu Zhao[5], Shuntaro Yamada[6], Niyaz Al-Sharabi[6], Kamal Mustafa[6], Pål R. Njølstad[1,7], Melina Claussnitzer[1,8,9,10], Roger D. Cox[4], Pierre Chymkowitch[5*], Gunnar Mellgren[1,2,3*†] and Simon N. Dankel[1,2,3*†]

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Vasiliki Lagou

University of Surrey

Highly commended poster No: 3

Title: Multi-phenotype GWAS uncovers shared genetic loci between type 2 diabetes, BMI, and four cancers

Ayse Demirkan1, Igor Pupko1, Vasilki Lagou1, Liudmila Zudina1, Zhanna Balkhiyarova1, Anna Ulrich1, Vincent Pascat2, Jared Maina2, Marika Kaakinen1,3, Inga Prokopenko1,2.

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2. Institut Pasteur de Lille, CNRS, University of Lille, Lille, France

3. Imperial College London, London, UK

Introduction: There are established relationships between type 2 diabetes (T2D) and cancer. In fact, cancer is the most common cause of death among patients with diabetes. We aimed to elucidate the pathophysiological processes shared between T2D, BMI and four cancers through multi-phenotype genome-wide association studies (MPGWAS).
Methods: We combined GWAS on 36,173 individuals from the European Prospective Investigation into Cancer, including 10,855 T2D, 4,126 postmenopausal breast, 2,111 colorectal, 473 pancreatic and 419 prostate cancer cases with pooled controls from all disease cohorts, imputed against the Haplotype Reference Consortium reference panel. We performed MPGWAS using the reverse regression approach as is implemented in the SCOPA software. For the top loci we evaluated the phenotype combinations driving the associations using Bayesian Information Criterion (BIC).
Results: Within MPGWAS, we identified 193 association signals (P<5x10-8) either for T2D-cancers or BMI-cancers models. Out of the 24 signals which were established for at least one of the included phenotypes, we classified *DND1P1* (for BC+T2D) and *PTHLH* (5 disease model, 4 disease and BMI model) as multi-phenotype loci, contributing to disease comorbidity. Of the remainder, we re-classified seventeen established loci, with primary effects on either on T2D, BMI and four cancer individual outcomes.
Interpretation Through the improved power via implementation of MPGWAS we highlighted a clear contribution of *DND1P1* explaining multi-phenotype effects underlying co-occurrence of breast cancer and diabetes and *PTHLH* effecting five diseases in addition to BMI.
Funding: WCRF-2017/1641, DIABETESUK 20/0006307, LONGITOOLS H2020-SCI-2019-874739

Marcel den Hoed

Uppsala University

Highly commended poster No: 4

Characterising the role of 46 candidate genes in early-stage atherosclerosis using live fluorescence imaging

Endrina Mujica[1], Anastasia Emmanouilidou[1], Hanqing Zhang[1], Eugenia Mazzaferro[1], Christoph Metzendorf[1], Manoj Bandaru[1], Naomi Cook[1], Ghazal Alavioon[1], Djordje Djordjevic[2], Sara Gry Vienberg[2], Anders Larsson[3], Amin Allalou[4], Marcel den Hoed[1]

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INTRODUCTION: Genome-wide association studies identified hundreds of loci associated with coronary artery disease (CAD). For most loci, causal genes remain uncharacterised. We use CRISPR/Cas9 and fluorescence microscopy in zebrafish larvae to systematically characterise the role of genes *in vivo*.

METHODS: One human candidate gene at a time (n=46), we targeted all zebrafish transcripts using CRISPR/Cas9, in fertilised eggs from zebrafish carrying transgenically expressed fluorescent labels on macrophages, neutrophils, and an antibody that binds oxidised LDL (oxLDL). Larvae were overfed from day 5 to 10, before live imaging using semi-automated fluorescence microscopy. Vascular accumulation/co-localisation of moieties was quantified using deep learning-based neural networks for image analysis. On average, we imaged 95 affected larvae and 75 sibling controls per gene (n_{total} 9537). For each trait (n=17), the effect of gene perturbation was examined using linear regression.

RESULTS: For 23 genes, perturbation affects at least one vascular trait. Mutations in *il1b* (encoding canakinumab's target) result in 2.8±1.1 SD units less vascular co-localisation of lipids and neutrophils; mutations in *slc5a2* (encoding SGLT2 inhibitors' target) result in 0.7±0.3 SD units less vascular co-localisation of oxLDL and macrophages. Genes affecting vascular traits are enriched for common variant associations with CAD in humans. For 14 of 23 genes, pLOF variants or drugs influence atherosclerosis in humans or mice with 79% directional consistency to our results.

INTERPRETATION: Characterising candidate genes for a role in early-stage atherosclerosis using zebrafish larvae can bridge the gap between genetic discovery in humans and in-depth characterisation of putative causal genes in larger animals.

KEY WORDS: *CRISPR/Cas9, zebrafish larvae, deep learning, automated fluorescence microscopy, common and rare variants.*

Yun Huang

University of Copenhagen

Highly commended poster No: 5

Genetic determinants of the plasma lipidome and relations to cardiometabolic risk in children and adolescents

Yun Huang[1], Sara E. Stinson[1], Malte Thodberg[1], Louise Aas Holm[1,2], Roman Thielemann[1], Karolina Sulek[3], Morten Asp Vonsild Lund[2,4], Cilius E. Fonvig[1,2,5], Min Kim[3], Kajetan Trost[1,3], Helene Bæk Juel[1], Trine Nielsen[5,6], Peter Rossing[3,5], Maja Thiele[7,8], Aleksander Krag[7,8], Cristina Legido Quigley[3,9#], Jens-Christian Holm[1,2,5#], Torben Hansen[1#]

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Background/Objectives: Several lipid species have been associated with type 2 diabetes, cardiovascular disease, and steatotic liver disease. While the genetic architecture of the lipidome has been investigated in adults, the genetic determinants of lipid species and their association with cardiometabolic risk in children and adolescents remain understudied.

Methods: We measured 227 plasma lipid species in 1,149 children and adolescents (44.8% boys) with a median age of 11.2 years from an obesity clinic and the general population. We performed genome-wide association analyses to identify genetic variants influencing circulating lipids and assessed the causal impact of these lipids on cardiometabolic risk profiles using Mendelian randomization (MR).

Results: We identified 37 independent genome-wide significant loci ($P < 5 \times 10^{-8}$) for 52 lipid species, including loci associated with sphingolipids (*SPTLC3*, *SYNE2*, *ATP10D*), phosphatidylethanolamine (*LIPC*), phosphatidylinositol (*MBOAT7*), and 9 previously unreported loci. One-sample MR analysis using 5 loci with biological plausibility on individual-level data identified positive causal associations between ceramide and liver enzymes, sphingomyelin and hemoglobin A1c (HbA1c), and phosphatidylethanolamine and high-sensitivity C-reactive protein in children and adolescents. Two-sample MR using summary statistics showed consistent results with one-sample MR, and indicated additional causal links, specifically between ceramide and higher HbA1c levels, and phosphatidylinositol with higher liver enzymes.

Interpretation: Our results provide insights into the genetic determinants of plasma lipid species in children and adolescents, emphasizing causal links between specific risk lipids and cardiometabolic risk profiles, which may provide further insights into targeted intervention strategies.

Adina Lupu

University of Bergen

Highly commended poster No: 6

Title: Genetic variants influencing BMI development in early childhood

Authors: Adina Elena Lupu[1], Jonas Hodneland Sundfjord[1], Nicolas Fragoso Bargas[1], Roya Karimi[1], Pål R. Njølstad[1], Marc Vaudel[1], Stefan Johansson[1].

[1]Mohn Center for Diabetes Precision Medicine, Department of Clinical Science, University of Bergen, Bergen, Norway,

Introduction: We previously identified 46 genomic loci associated with childhood BMI in the Norwegian Mother, Father, and Child-Birth cohort (MoBa) and showed that the architecture changes over time.

Methods: We performed GWAS in 66 000 children for 12 time points from birth to 8 years old and applied FUMA along with LD score regression and PRS.

Results: We observe 197 loci at GWS, a fourfold increase in associations with BMI from birth to 8 years in the new data release. The highest number of independent SNPs peaks between 6 months and 1 year of age, around the adiposity peak (AP) (n=118 at 6 month). The genetic correlation between BMI at the AP and later in life is relatively weak (rg=0.39 with BMI 8 years and rg=0.21 with adult BMI) suggesting that BMI in infancy is mainly controlled by genetic variation different from later in life. The time-dependent PRSs derived from MoBa outperforms other BMI PRSs and explains approximately 10% of the variation in BMI at the AP in ALSPAC children.

Computational functional analyses identify gene expression enrichment in tibial nerve at age 6 months and the H3K36me3 chromatin mark in adrenal glands at age 8 months. Also, BMI-signals at age 8 months overlapped more often with adult signals for hip circumference and waist-to-hip ratio rather than adult BMI.

Interpretation: The observed genetic signals coincide with the AP, conveying that this time point is governed by specific genetic and biological events involved in the shaping of infants' BMI and adiposity control.

Timothy Hall

University of Exeter

Highly commended poster No :7

Large-scale blood mitochondrial genome wide associations study provides novel insights into diabetes

Timothy Hall[1*], Stuart Cannon[1,2*], Gareth Hawkes[1], Michael N Weedon[1,2], Kashyap A Patel[1,2]

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Introduction

Mitochondrial DNA variants can lead to multi-system disorders including diabetes. We aimed to perform the first large-scale, hypothesis-free mitochondrial genome-wide association study to identify mitochondrial DNA variants associated with diabetes.

Methods

We identified common, rare, and previously reported pathogenic mitochondrial variants using MitoHPC software on whole genome sequencing data from 164,708 individuals of European ancestry in the UK Biobank cohort. We used REGENIE software to test all mitochondrial variants with ≥3% or ≥97% heteroplasmy for association. The significance threshold was $P < 4x10-7$.

Results

We found 7,467 variants among 164,708 individuals. Only m.3243A>G (n=79) reached genome-wide significance for association with diabetes (odds ratio=5.6, $P = 3x10-9$). The association with diabetes was stronger with higher m.3243A>G heteroplasmy (OR 8.6 and 25 for 5% and 10%, respectively; $P < 3.3x10-11$). m.3243A>G also associated with hearing loss (OR 12.3, 95% CI [6.2–24.4], $P = 6×10−13$) and heart failure (OR 39.5, 95% CI [9.76–160.1]; $P < 3×10−7$). The risk of diabetes with m.3243A>G was further modified by T2DGRS. For m.3243A>G carriers, diabetes risk at 50 years increased from 5% (95% CI [1–29]) to 14% (95% CI [4–46]) to 29% (95% CI [14–53]) for people with low, medium and high T2DGRS tertiles, respectively. No other known pathogenic variants or rare variant aggregations identified novel associations.

Interpretation

m.3243A>G associates with diabetes in a heteroplasmy-dependent manner, which can be modified by nuclear genomic variants. Expansion to 500,000 individuals is underway to identify potential novel associations.

Lucas Maurin

University of Lille

Highly commended poster No: 8

Epigenetics is a key driver for islet dysfunction linked to age

Lucas Maurin[1], Lorella Marselli[2], Lijiao Ning[1], Mathilde Boissel[1], Mark Ibberson[3], Miriam Cnop[4], Amélie Bonnefond[1], Piero Marchetti[2], Philippe Froguel[1,5], Amna Khamis[1,5]

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Introduction:

Aging is the main risk factor for type 2 diabetes (T2D), partly due to the loss of functional pancreatic islets. We hypothesised that epigenetic mechanisms contribute to β-cell dysfunction.

Methods:

We assessed 144 pancreatic islets obtained from organ donors, of which 21 had T2D (age range=22-96). We generated DNA methylation (methylationEPIC 850K arrays) data and performed epigenome wide association studies (EWAS) with age and T2D. Transcriptomics data (RNA sequencing) was generated to identify CpGs influencing nearby gene expression, and also differentially expressed by the relevant phenotype (*i.e.,* age or T2D).

Results:

Our EWAS revealed 1,151 CpGs associated with age, of which the vast majority (85%) were hypermethylated with increased age. Of these CpGs, 679 (45%), were associated with nearby gene expression, of which 236 genes were also directly associated with age. Pathway analysis revealed an enrichment of genes involved in chromatin remodelling, a key mechanism in β-cell decline and several genes implicated in insulin secretion, *i.e., ELOVL2,* and *GNPNAT1*. To address the effect of T2D exposure on islet age, we applied Horvath's biological clock and found that T2D individuals exhibited accelerated biological aging. Therefore, we performed an EWAS for T2D and identified 952 CpGs associated with T2D, of which 622 (65%) implicated nearby genes, however, none were associated directly with T2D.

Interpretation:

Age induces DNA methylation changes with functional consequences in islets, specifically in chromatin remodelling, suggesting that epigenetics is a major environmental driver of age-mediated β-cell decline. The impact of T2D on islets epigenetics remains unclear.

Lauriane Le Collen

EGID Ligan team, Lille

Highly commended poster No: 9

Pathogenic Heterozygous Variants of *LEPR* Do Not Cause Monogenic Obesity: Therapeutic Implications

Lauriane Le Collen [1-5], Jérôme Delplanque[1,2], Audrey Leloire[1,2], Hélène Loiselle[1,2], Beverley Balkau[6], Michel Marre[7], Mehdi Derhourhi[1,2], Philippe Froguel[1,8], Amélie Bonnefond[1,8]

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Introduction. Obese patients with a deficiency in the leptin pathway due to biallelic pathogenic *LEPR* variants can benefit from the MC4R agonist (setmelanotide). An ongoing phase 3 clinical trial (NCT05093634) includes patients with obesity who carry a heterozygous *LEPR* mutation, although the obesogenic impact of these mutations remains incompletely evaluated. The aim of this study was to evaluate the effect of heterozygous pathogenic variants in *LEPR* in obesity.

Methods. We sequenced *LEPR* in ~10,000 participants from the French RaDiO study. Each identified variant was investigated in vitro. The pathogenicity was determined according to the criteria of the American College of Medical Genetics and Genomics (ACMG), including the functional assays. Association between pathogenic *LEPR* variants and obesity was done. We analyzed the clinical phenotype of heterozygous carriers in the Human Gene Mutation Database (HGMD) and UK Biobank (200K).

Results. 86 rare heterozygous variants of *LEPR* were identified in the RaDiO study, with no biallelic variants. Following functional analyses of each variant, 14 were found pathogenic. Most carriers had a normal weight and we found no association between the pathogenic variants and BMI. This lack of association between pathogenic *LEPR* variants and obesity/BMI was confirmed in the UK Biobank. In HGMD, 36 rare heterozygous pathogenic *LEPR* variants were identified, with 44% of carriers exhibiting a normal weight.

Interpretation. Pathogenic heterozygous *LEPR* mutations, though functionally recognized, do not increase obesity risk. The utilization of the costly setmelanotide in patients with obesity based on the presence of a heterozygous *LEPR* variant raises question.

Laura Kind

University of Bergen

Highly commended poster No: 10

The molecular mechanism of HNF-1A mediated *HNF4A* gene regulation and promoter-driven HNF4A-MODY diabetes

Laura Kind[1], Janne Molnes[2, 3], Erling Tjora[2, 4], Arne Raasakka[1], Matti Myllykoski[1], Kevin Colclough[5], Cécile Saint-Martin[6, 7], Caroline Adelfalk[8], Petra Dusatkova[9], Stepanka Pruhova[9], Camilla Valtonen-André[10], Christine Bellanné-Chantelot[6, 7], Thomas Arnesen [1, 11]*, Petri Kursula[1, 12] & Pål Rasmus Njølstad [2, 13]*

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Introduction:
Hepatocyte nuclear factor 1A (HNF-1A) and HNF-4A are transcription factors that engage in gene transcription networks to maintain glucose-stimulated insulin secretion in pancreatic β-cells. *HNF1A* and *HNF4A* variants are associated with maturity-onset diabetes of the young (MODY). Here, we explored four variants in the P2-*HNF4A* promoter, three in the HNF-1A binding site and one close to the site. Our goal was to study the disease causality for these variants and to investigate diabetes mechanisms on the molecular level.

Methods:
We collected clinical data from different MODY registries across Europe and analyzed diabetes phenotypes of P2-*HNF4A* promoter variant carriers. We employed X-ray crystallography to study the binding of recombinant HNF-1A to the P2-*HNF4A* promoter. By utilizing ITC and BLI, we assessed the impact of promoter variants on HNF-1A DNA recognition. We complemented the *in vitro* results with transactivation assays, demonstrating how P2-*HNF4A* promoter variants affect HNF-1A activity in cells.

Results:
We solved a novel crystal structure of HNF-1A bound to the P2-*HNF4A* promoter and established a set of techniques to probe HNF-1A interaction with different promoter variants. We found changes in HNF-1A binding or transcriptional activity for all four variants. The results suggest distinct disease mechanisms of the promoter variants, which can be correlated with clinical phenotype.

Interpretation:
Our study serves as an example how biochemical and structural biology methods can contribute to the functional analysis during variant interpretation. Knowledge of the mechanistic and phenotypic differences between the studied P2-*HNF4A* promoter variants will be valuable for clinical utility in precision diabetes medicine.

Steven Squires

University of Exeter

Highly commended poster No: 11

Comparing three type 1 diabetes genetic risk scores on diverse ancestry populations

Steven Squires[1], Jean Claude Katte[1], Dana Dabelea[2], Catherine Pihoker[3], Jasmine Divers[4], William Hagopian[5], Andrew Hattersley[1], Michael N. Weedon[1], Angus Jones[1], Richard A. Oram[1]

Introduction: Genetic risk scores (GRS) for type 1 diabetes (T1D) show high discriminative power but are often generated from European populations and may not perform as well on underrepresented groups. To improve health outcomes and reduce inequalities it is important to understand the performance of GRSs on different ancestries and how to apply them.

Methods: We apply three GRSs, two developed from European ancestry populations (denoted as GRS30 and GRS67) and one from an African ancestry population (denoted as GRS7), to T1D and non-T1D data from African, European, and Hispanic populations in the USA and two sub-Saharan Africa populations from Cameroon and Uganda.

Results: The discriminative power, as measured by the area under the receiver operating characteristic (AUC), for GRS67 and GRS7 are equivalent on the African ancestry populations and both perform better than the GRS30. For example, the AUCs produced by the GRS67, GRS7 and GRS30 on the Ugandan data are 0.890 (0.848-0.925), 0.879 (0.836-0.918) and 0.800 (0.741-0.856) respectively. On the Hispanic and European populations the GRS67 outperforms the GRS7 and GRS30. The distribution of GRS67 varies significantly for different populations with lower average scores for the African populations than the Hispanic or European populations.

Interpretation: The GRS67 produces either similar or improved discriminative power across the populations as the other GRSs. As the distributions of GRS67 scores vary with populations different thresholds defining different levels of risk may be required and care needs to taken when making comparisons across populations to avoid misjudging T1D risk and model performance.

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Russell Donis

University of Exeter

Highly commended poster No: 12

A homozygous *TARS2* variant is a novel cause of neonatal diabetes, epilepsy and developmental delay

Russell Donis[1]; Matthew N Wakeling[1]; Michael N Weedon[1]; Kashyap A Patel[1]; Andrew T Hattersley[1]; Sarah E Flanagan[1]; Elisa de Franco[1]

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Introduction:

Neonatal Diabetes is a monogenic disease which can be the presenting feature of complex syndromes. The aim of this study was to identify novel genetic causes of neonatal diabetes syndromes with early neurological features including developmental delay and epilepsy.

Methods:

We performed whole-genome-sequencing (WGS) in 27 individuals diagnosed with neonatal diabetes plus epilepsy and/or developmental delay. All known neonatal diabetes causes had been excluded. Genes with novel/rare coding variants in at least 3 probands were followed-up. Replication studies using targeted next-generation-sequencing were performed in 195 individuals with diabetes diagnosed before 12 months of age without a known genetic cause.

Results:

Three individuals shared a rare homozygous missense variant, p.(Arg327Gln), in the *TARS2* gene. Replication studies identified the same homozygous variant in a 4th individual. Haplotyping showed that 3/4 individuals shared a distant ancestor.

Median age at diagnosis of diabetes was 39 days and birth weight Z-score range was -4.72 – -1.90. All 4 probands had epilepsy and 3 had documented developmental delay. Three individuals had lactic acidosis consistent with mitochondrial dysfunction. All 4 individuals died before 12 months of age.

Biallelic *TARS2* variants cause COXPD21, a mitochondrial encephalopathy. Diabetes has not been previously reported as a clinical feature in individuals with *TARS2*-related disease.

Interpretation:

Our findings establish *TARS2* as a novel aetiological gene for neonatal diabetes and expand the clinical spectrum of *TARS2*-related disorders. Testing for *TARS2* is recommended in individuals with neonatal diabetes, especially those with additional neurological features.

Posters

Amber Luckett

University of Exeter

Poster No: 13

Type 1 diabetes polygenic risk contributes to phenotypic presentation in monogenic autoimmune diabetes

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Introduction:

Disease causing variants in key immune homeostasis genes can lead to monogenic autoimmune diabetes. These individuals present with highly variable syndromes of autoimmunity however the mechanism underlying this variability is not understood. We aimed to determine whether type 1 diabetes (T1D) polygenic risk contributes to phenotypic presentation in monogenic autoimmune diabetes.

Method:

We used the 67 SNP T1D genetic risk score (GRS) model to determine polygenic risk in 63 individuals with monogenic autoimmune diabetes (*AIRE* n=3, FOXP3 n=36, *IL2RA* n=5, *STAT3* n=7*, TNFAIP3* n=1*,* and *LRBA* n=11) and 200 non-autoimmune neonatal diabetes (NDM) controls (*ABCC8* n=22, *KCNJ11* n=70, *INS* n=74, *EIF2AK3* n=34). We used population-based controls without diabetes (n=10,405) as a comparator.

Results:

Individuals with monogenic autoimmune diabetes had higher GRS (mean 11.28; 95% CI 10.75-11.82) vs. non-autoimmune NDM (mean 9.72; 95% CI 9.40–10.04, P=9.04x10^{-6}) or controls (mean 10.26; 95% CI 10.22–10.31, P=8.97x10^{-4}). This was driven by monogenic autoimmune diabetes cases having higher Class II HLA genetic risk score (mean= 0.36 vs. NDM -0.78, P=9.86x10^{-6}) due to higher frequency of the *DR3*/*DQ2.5* T1D risk haplotype (P= 1.20x10^{-15}). We saw similar results when restricting analysis to individuals of European ancestry only. A GRS cut-off based on 25th centile of T1D cases would identify 89% of monogenic diabetes for gene discovery studies.

Interpretation:

Polygenic risk, particularly HLA class II, likely contributes to clinical presentation in monogenic autoimmune diabetes. Despite this, the GRS remains useful in identifying monogenic autoimmune diabetes cases from more common polygenic autoimmune diabetes.

Valérie Schwitzgebel

University of Geneva

Poster No: 14

Transcriptomic Insights into Meal-Induced Pathway Activation in Youth with Monogenic and type 1 Diabetes

Ingrida Stankute[1], Cedric Howald[2], Kathrin Männik[2], Ioannis Xenarios[2], Jean-Louis Blouin[3,5], Rasa Verkauskiene[6], Rimante Dobrovolskiene[1], Evalda Danyte[6], Dovile Razanskaite-Virbickiene[6], Edita Jasinskiene[1], Giedre Mockeviciene[1], Valerie M. Schwitzgebel[7,8]

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Introduction: Diabetes encompasses a diverse array of metabolic disorders, each characterized by unique pathophysiological processes. This study aims to elucidate the gene regulation pathways altered in youths with Maturity Onset Diabetes of the Young (MODY) and Type 1 Diabetes (T1D) compared to healthy controls in response to a meal.

Methods: A standard mixed-meal tolerance test (MMTT) was conducted to observe glucose and C-peptide fluctuations in children diagnosed with MODY, T1D, and in healthy controls. RNA expression profiles were assessed pre-meal and at 120 minutes post-meal. The analysis of RNA sequencing data utilized GENCODE software to interpret the results.

Results: The study enrolled 15 participants with MODY (8 with GCK mutations), 22 with T1D, and 10 healthy controls. Analysis revealed 21 differentially regulated transcripts in healthy controls post-MMTT. Of these, 18 meal-responsive genes were identified as protein-coding and consistently differentially regulated across all healthy participants. Functional enrichment analysis highlighted pathways such as cytokine production, toll-like receptor binding, and eicosanoid binding. Comparatively, in T1D versus controls, 107 genes were differentially expressed (55 upregulated, 52 downregulated), primarily involved in antigen binding. The comparison between T1D participants and those with *GCK* mutations revealed 27 differentially expressed genes, implicated in antigen binding and the maintenance of endoplasmic reticulum homeostasis.

Conclusion: This investigation uncovered distinct meal-induced transcriptional responses among individuals with MODY and T1D. These findings suggest that the pathophysiological divergence between MODY and T1D extends to differential gene regulation in response to nutritional stimuli, offering insights into the complex metabolic adaptations present in these conditions.

Alice Williamson

Queen Mary University of London

Poster No: 15

Genetic architecture of fat and lean mass across body compartments in men and women

Alice Williamson[1,2], Laura B L Wittemans[3,4,2], on behalf of the Body Composition Genomics Consortium

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Disclosures: Laura B L Wittemans is now an employee of Novo Nordisk.

Introduction: Genetic analyses of overall adiposity and fat distribution have primarily focused on simple measures of body size (e.g., body mass index; BMI) or fat distribution (e.g., BMI-adjusted waist-hip ratio; WHR), important contributors to cardiometabolic disease risk. However, these simple measures do not explain the full spectrum of fat distribution across all body compartments nor consider lean mass. Dual X-ray absorptiometry scans (DEXA) provide greater insight into regional body composition.

Methods: We conducted fixed-effect genome-wide association study (GWAS) meta-analysis for 31 DEXA-derived regional fat and lean mass traits, including 74,554 individuals of European ancestry across 7 studies. Sex-stratified GWAS analyses allowed identification of sex-dimorphic loci. Cross-ancestry comparison included an additional 4,701 individuals of Qatari ancestry.

Results: We identified 679 independent signals ($P<5x10^{-8}$) after cross-trait fine mapping. Of these, 384 were specific to fat mass compartments, with limited overlap with signals for commonly used measures such as BMI (8%) or BMI adjusted WHR (48%), despite their much larger sample sizes. In Qatari-only analyses, 372 of these loci also had a significant signal ($P<5x10^{-5}$). We identified substantial differences in genetic effects between sexes on large body compartments, specifically peripheral fat distribution in the legs. Deep molecular and clinical phenotyping identified subsets of loci with distinct metabolic effects on human health.

Interpretation: This is the first large-scale study to identify the complex genetic architecture and sex differences of both fat and lean mass. This study demonstrates the value in going beyond simple indices to investigate the mechanisms influencing body composition.

Roman Thielemann

University of Copenhagen

Poster No: 16

Title: Causal effects of the plasma proteome on childhood health

Authors:

Roman Thielemann[1], S. E. Stinson[1], Y. Huang[1], L. A. Holm[1,2], JC. Holm[2], S. Rasmussen[1], T. Hansen[1]

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Introduction:

Protein quantitative trait loci (pQTL) studies in pediatric populations remain limited. PQTLs combined with Mendelian randomization can infer causal effects of proteins on health and disease. Here, we use genetic and proteomic data from The HOLBAEK Study, a cohort of 3,811 Danish children and adolescents, to 1) identify plasma pQTLs in childhood and adolescence and 2) examine changes in pQTLs across the lifespan.

Methods:

We performed genome-wide association studies for 184 plasma proteins measured with Olink proteomics in 3,811 children and adolescents (44.2% boys) with a median age of 11.7 years. Participants were recruited from an obesity clinic (n=1,773) and a population-based cohort (n=2,038). We assessed gene-environment interactions with overweight and pubertal status. Lead pQTLs were matched and compared with adult data from the UK Biobank Pharma Proteomics Project.

Results:

We identified 1,448 independent, genome-wide associations for 184 proteins in children and adolescents. For several variants, gene-environment interactions with overweight and pubertal status were observed. Matched pQTLs explained a similar proportion of variance (PVE) in The HOLBAEK Study and the UK Biobank, but for several proteins, PVE differed across age.

Interpretation:

We performed a large-scale Olink pQTL study in children and adolescents. PQTLs explained similar proportions of variation in plasma protein levels in adults and children, but several proteins exhibited large differences in PVE across age. In ongoing studies, we use Mendelian Randomization to identify proteins with causal effects on cardiometabolic traits. This study will elucidate causal disease mechanisms of cardiometabolic risk and obesity in early life.

Thomas Koefoed

University of Copenhagen

Poster No: 17

Title

Investigating the link between human skeletal muscle fiber type composition and insulin resistance

Authors

Thomas G. Koefoed[1], Sufyan Suleman[1], Benedicte S. Kapel[1], Laura M. Pikkupeura[1], Malte Thodberg[1], Anne Cathrine B. Thuesen[1], Kata Krizic[1], Rikard G. Fred[1], Torben Hansen[1], and Niels Grarup[1]

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Introduction

Despite considerable efforts to map the complex characteristics of insulin resistance (IR), the link between skeletal muscle fiber type composition and IR is still poorly characterized. In this study, we use bulk and single-cell level transcriptomic data in an effort to close this gap in knowledge.

Methods

We generated bulk-level transcriptomic data from skeletal muscle biopsies (vastus lateralis) of 127 individuals who had previously undergone an oral glucose-tolerance test to determine their degree of IR. Using these data, we performed differential gene expression analyses to detect associations between gene expression in muscle tissue and IR. Additionally, we generated single-cell transcriptomic data to deconvolute the bulk-level data and detect associations between IR and muscle fiber type composition.

Results

Several marker genes for fast-twitch fibers were found to be significantly upregulated with increasing IR, while marker genes for slow-twitch fibers were significantly downregulated with increasing IR. In the single-cell deconvoluted bulk data, we found statistically significant differences in the ratio of fast-to-slow myocyte nuclei abundances between groups of individuals with low, medium, and high IR.

Interpretation

The observed associations between muscle fiber type marker expression and IR confirm previous findings that IR and skeletal muscle fiber composition is tightly linked. This was further supported by the single-cell deconvoluted bulk-level data. In the future, we aim to generate additional single-cell data to further explore these results in detail. Finally, we are also exploring the use of mendelian randomization to determine the direction of causality between IR and skeletal muscle fiber composition.

James Russ-Silsby

University of Exeter

Poster no: 18

ZNF808 Loss of Function Variants Result in a Broad Spectrum of Diabetes Phenotypes

James Russ-Silsby[1], Matthew B Johnson[1], Matthew N Wakeling[1], Kashyap Patel[1], Kevin Colclough[2], Nick DL Owens[1], Sarah E Flanagan[1], Andrew T Hattersley[1], Elisa De Franco[1]

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(250/250 words)

Introduction
Loss-of-function (LoF) variants in the primate-specific gene *ZNF808* were recently identified to cause pancreatic agenesis. The aim of this study was to explore the role of *ZNF808* LoF variants in a large cohort of individuals with monogenic diabetes to characterise the clinical phenotype caused by this new genetic aetiology.

Methods
ZNF808 was analysed in 4,391 individuals with clinically suspected monogenic diabetes (including 398 diagnosed <12 months) using a targeted next-generation-sequencing assay or whole-genome-sequencing.

Results
We identified 28 individuals (13 previously published) with 18 different biallelic *ZNF808* LoF variants, including 3 deletions predicted to result in mRNA degradation and 15 protein-truncating variants (PTVs).

25/28 individuals had diabetes diagnosed before 1 year, with 18/28 (64%) diagnosed before 6 months. The further 3 individuals had diabetes onset after 1 year: at 10, 14, and 23 years. 6 individuals were not insulin-treated, with diabetes remission being reported in 4 individuals (median remission age 2 years, range 12 weeks – 3 years) and 2 being treated with oral hypoglycemic agents. Low birthweight was common, with 27/28 individuals born small for gestational age (median birthweight Z-score -4.19), indicating absent insulin secretion in utero similar to other pancreatic agenesis genes.

Notably, two PTVs, located in the 14th and 15th Zinc-Finger domains, occurred in 4 individuals, all with transient/later-onset diabetes, suggesting a possible genotype-phenotype relationship.

Interpretation
Our findings establish biallelic *ZNF808* LoF variants as a cause of transient and later-onset diabetes in addition to pancreatic agenesis, highlighting the broad diabetes spectrum caused by loss of this primate-specific gene.

Pauline Kromann Reim

University of Copenhagen

Poster No: 19

The Interplay between Birth Weight and Obesity in Determining Childhood and Adolescent Cardiometabolic Risk

Authors

Sara Elizabeth Stinson, PhD[1], Pauline Kromann Reim, MD[1], Morten Asp Vonsild Lund, MD[2,3], Ulrik Lausten-Thomsen, PhD[4], Louise Aas Holm, MD[1,2], Yun Huang, MSc[1], Charlotte Brøns, PhD[5], Allan Vaag, PhD[3,5], Maja Thiele, PhD[6,7], Aleksander Krag, PhD[6,7], Cilius Esmann Fonvig, PhD[1,2,8], Niels Grarup, DMSc[1], Oluf Pedersen, PhD[1,9], Michael Christiansen, PhD[3,10], Lars Ängquist, PhD[1], Thorkild I.A. Sørensen, DMSc[1,11,12], Jens-Christian Holm, PhD*[2,8], Torben Hansen, PhD*[1]

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Introduction: Birth weight (BW) is associated with risk of later cardiometabolic disease (CMD), which may depend on the state of obesity throughout the life course. We hypothesized that BW and a polygenic score (PGS) for BW were associated with cardiometabolic risk and related plasma proteins, and aimed to determine the modifying effect of childhood obesity.

Methods: We used data from The HOLBAEK Study consisting of 4,263 4–20-year-olds. We gathered information on BW, anthropometrics, and measures of cardiometabolic risk factors, calculated a PGS for BW, and measured plasma proteins using Olink Inflammation and Cardiovascular II panels. To assess the associations between BW, BW PGS and cardiometabolic risk factors, we employed multiple linear regression. We performed interaction analyses to assess the effect of childhood obesity.

Results: BW positively associated with anthropometrics and adiponectin, but negatively with other cardiometabolic risk factors. BW PGS demonstrated consistent direction of effects, with positive associations with anthropometric traits and negative associations with several cardiometabolic risk factors. BW was positively associated with plasma levels of 3 proteins (CX3CL1, TWEAK, LPL) and negatively associated with 16 proteins (e.g. FGF-21, HOAX1, leptin). The negative associations between BW and measures of insulin resistance were more pronounced in individuals with obesity.

Interpretation: Our findings substantiate that the association between lower BW and increased CMD risk is present before adulthood. The associations between lower BW and adverse metabolic phenotypes, particularly insulin resistance, seem more pronounced in the presence of childhood obesity.

Augusto Santomauro

University of São Paulo

Poster No: 20

Genotypic Diversity in Brazilian Wolfram Syndrome: A Monogenic Diabetes Clinic Study

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Introduction: Wolfram syndrome (WFS) is a rare neurodegenerative disorder that figures into differential diagnoses for hyperglycemia in childhood. Decoding the molecular underpinnings of WFS are imperative for developing effective treatments and enhancing life quality for those affected by this disease.

Methods: This study examined 10 unrelated individuals (7 females) diagnosed with WFS at our Monogenic Diabetes Clinic, representing diverse Brazilian regions. We gathered clinical and laboratory data including gender, age at diabetes mellitus (DM) diagnosis, age at diagnosis of other comorbidities, parental consanguinity, insulin requirement, and A1C levels at initial consultation. Analysis spanned from 2015 to 2023.

Results: The median current age of the patients is 24.1 years, with a range of 15 to 31 years. Diagnosis of DM was consistently made in the first decade of life (median age: 5.3 years, range 3.5 to 9 years). Seven patients developed central diabetes insipidus in their second decade, along with optic atrophy. Six patients experienced sensorineural hearing loss. Eight exhibited compound heterozygous variants in the *WFS1* gene, with the p.Val412Serfs*29 variant recurring in four individuals. The average A1C at referral was 9.4%, with a mean insulin requirement of 0.82 UI/kg.

Interpretation: The correlation between the identified mutations and clinical manifestations remains ambiguous. Our Brazilian cohort aligns with international cases in terms of clinical presentation yet exhibits a greater incidence of compound heterozygosity and a higher mean age. Highlighting our cohort's phenotypic and genotypic variations is essential to refine prognoses and customize WFS treatment.

Zuzana Dobiasova

Slovak Academy of Sciences

Poster No: 21

T1D GRS: a tool for identifying patients with monogenic diabetes

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Introduction: The Genetic Risk Score for Type 1 Diabetes Mellitus (T1D GRS) can help in differentiating T1D from other types of diabetes. **Our aim** was to determine the T1D GRS in children with newly diagnosed diabetes, to determine its discriminatory power in the Slovak population, and to use it as an additional marker for picking individuals for monogenic diabetes genetic testing.

Methods: We included 759 children with clinically suspected diabetes and 204 control subjects (179 patients with monogenic diabetes and 25 healthy controls) whose DNA was analysed using the Infinium Global Screening Array MD v3. We calculated 10, 30, and 67 SNP T1D GRS. Monogenic diabetes genetic testing included MLPA and NGS panel.

Results: After follow-up, diagnosis of T1D was excluded in 33 individuals from the group of newly diagnosed children (T2D, stress- or corticoid-induced hyperglycaemia, or diabetes not confirmed). Therefore, T1D was suspected in 726 children and the control group was increased to 237 individuals. The 67 SNP T1D GRS was the most discriminative with ROC-AUC=0.92. T1D GRS values over the cut-off 9.9 (> 14 T1D centile) were indicative of T1D (85.6 % specificity, 86.1% sensitivity). Genetic testing was performed in all Ab-negative cases and cases with T1D GRS below the cut-off. Until now, 4 GCK-MODY and 2 HNF1B-MODY cases were confirmed.

Interpretation: The T1D GRS, in addition to the currently used clinical criteria, could be another useful tool in the differential diagnosis of monogenic diabetes from T1D.

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Luke Sharp

University of Exeter

Poster No: 22

Prevalence, penetrance, mortality of monogenic lipodystrophy in the UK population – implication for routine clinical practice

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Background:

Monogenic lipodystrophy is important to diagnose because of high risk of metabolic disorders. However, its prevalence and clinical features outside the clinically selected cases are unknown. We aim to determine the prevalence, clinical features, penetrance and mortality in monogenic lipodystrophy cases in a large clinically unselected cohort.

Method:

We analysed 454,699 individuals (mean age 57) with whole exome sequencing from the population cohort UK Biobank. Pathogenic variants in all known monogenic lipodystrophy genes (generalised/partial) were identified according to ACMG guidelines. Lipid, adiposity, and diabetes traits were compared between cases and non-carriers. All-cause mortality was assessed over 14 years.

Results:

We identified 26 individuals with monogenic lipodystrophy, giving a prevalence of 1 in 17,488. Cases were associated with diabetes (16.8% penetrance by age 50, $p<0.0001$). Monogenic lipodystrophy cases had same BMI as noncarriers (26 vs 26.7, $p>0.2$) but cases had lower HDL (1.1 vs 1.5 mmol/L, $p<0.0001$), body fat percentage (24.3% vs 31%, $p<0.0001$), and higher triglycerides (2.5 vs 1.5 mmol/L, $p<0.0001$). Females appeared more severely affected. Only 7.7% of cases had values >1SD away from noncarriers in all three significantly different traits. Despite this milder phenotype, monogenic lipodystrophy cases had higher mortality than non-carriers by age 75 (31.3% vs 9.1%, $p<0.0001$).

Interpretation:

The prevalence of monogenic lipodystrophy is 1 in 17,448 in population. Clinically unselected Monogenic lipodystrophy cases have milder phenotype, however, remain at increased mortality risk. Our results suggest importance of diagnosis of even milder lipodystrophy in clinical practice for early treatment and prevention of metabolic disorders.

Kathryn Hinton

University of Exeter

Poster No: 23

98% of pancreatic agenesis cases are caused by variants disrupting gene regulation in development

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Introduction: Pancreatic agenesis (PA) is a rare congenital disorder resulting from failure of pancreas development, presenting as neonatal diabetes with exocrine insufficiency. Pathogenic variants affecting 8 genes, all regulators of transcription (*CNOT1, GATA4, GATA6, ONECUT1, PDX1, PTF1A, RFX6,* and *ZNF808*), are known to cause PA with phenotypic variability within and between genetic subtypes. Studying individuals with PA is important to characterise the disease's clinical course and gain insight into essential gene regulation during pancreatic development.

Methods: We assessed the genetic and clinical features of 130 individuals (from 125 families) with PA confirmed by MRI and/or biochemical analysis. The 8 PA genes were analysed by Sanger and/or next-generation sequencing (targeted, exome or genome sequencing) in all individuals.

Results: Disease-causing variants were identified in 122/125 probands (98%), and 4/5 affected siblings, most commonly recessive *PTF1A*-enhancer variants (44 probands, 35.2%), followed by *GATA6* haploinsufficiency (37/125, 29.6%). Variants in *PTF1A*, *PDX1*, *GATA4*, *RFX6*, *ZNF808,* and *CNOT1* were rarer. No *ONECUT1* variants were identified.

All individuals had low birthweight (median Z-score: -3.16) and early diabetes diagnosis (median age: 2 weeks), with no significant differences between aetiologies. 108/130 (83%) individuals had extra-pancreatic features. Cardiac malformations were most common (n=43) and associated with *GATA6* variants. Other common features included anaemia (n=18) and hepatic dysfunction (n=12).

Interpretation: Our study of the largest PA cohort to date characterises the genotypic and phenotypic variability of PA. Our finding that 98% of PA cases are caused by variants disrupting transcriptional regulators highlights their essential roles in human pancreas development.

Isabella Lazaridi

University of Exeter

Poster No: 24

Title
Copy Number Variants: An important cause of Hyperinsulinism that should be screened during routine testing

Authors
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Introduction
Congenital Hyperinsulinism (HI) results from inappropriate insulin secretion leading to hypoglycaemia. It can present in isolation or feature as part of a syndrome. Over 30 genetic aetiologies have been identified for this condition with routine screening identifying a pathogenic variant in ~50% of individuals.

6 different large (>1Mb) copy number variants (CNVs) which encompass multiple genes, are reported to cause HI but are often not routinely screened for in all individuals with HI. Consequently, the contribution of CNVs to the disease aetiology is unknown.

Methods
We studied an international cohort of 2,033 individuals with HI. These individuals had undergone targeted Next Generation Sequencing (n=1,614), genome sequencing (n=178) and microarray analysis (n=214). The 6 large CNVs known to cause HI were screened for in all individuals: Chr9p deletion, Chr20p11.2 deletion, monosomy X causing Turner syndrome, Chr11p15.5 deletion/duplication causing Beckwith-Wiedemann syndrome, Chr11p15.1 deletion causing Usher syndrome and Chr5q35 causing Sotos syndrome. We used internal controls (n=8,733) to exclude common CNVs.

Results
Large heterozygous CNVs were identified in 31/2,033 individuals (1.5%). This included 15 individuals with 9p deletions, 1 individual with an 11p15.5 duplication, 5 individuals with a 20p11.2 deletion and 10 female individuals with a large deletion on the X chromosome.

Interpretation
We have shown that large CNVs are an important cause of HI, accounting for 1.5% of diagnoses in our cohort (n=31/2,033). These findings demonstrate the importance of screening large CNVs during routine testing in order to provide more individuals with a genetic diagnosis.

Ankit Arni

University of Exeter

Poster No: 25

Beyond Arrays: Leveraging Whole Genome Sequencing on 149,265 individuals to provide insight into ancestry-specific Type 1 Diabetes risk in the population.

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Background:

Type 1 Diabetes Genetic Risk Score (T1DGRS) aids diagnosis and prediction of T1D. It is currently generated from array-genotypes imputed to a reference panel, known to be less accurate in non-European genetic ancestries. Conversely, Whole Genome Sequencing (WGS) offers the potential for T1DGRS generation across all ancestries without imputation. Our study aims to assess the disparities between WGS-based T1DGRS and the established array-based T1DGRS, with particular attention to variations across ancestries.

Methods:

We analysed 149,265 diverse ancestry individuals from UK Biobank with WGS and TOPMed-imputed array-genotypes (European/EUR=137,888; African/AFR=2,404; South Asian/SAS=3,346; Others/OTH=5,627). We compared the 67-variant T1DGRS along with its HLA/non-HLA components, derived from WGS versus imputed genotypes, in the whole cohort and stratified by ancestry.

Results:

Overall, WGS-based T1DGRS correlated strongly with array-based T1DGRS (r=0.99), with a slightly lower mean (-0.0028 SD, $p<10^{-31}$). However, this difference was 10-fold larger in non-EUR (AFR -0.018 SD, $p<10^{-14}$ and SAS -0.013 SD, $p<10^{-6}$).

At the clinically relevant T1DGRS threshold (>90th centile), array-based T1DGRS re-categorised 2.3% of high-risk individuals, exacerbated in non-EUR (AFR 11.7% and SAS 7.3%).

Ancestry stratification revealed that both AFR and SAS had lower WGS-based T1DGRS than EUR (-0.89 SD, $p<10^{-300}$ and -0.28 SD, $p<10^{-58}$). Applying the EUR >90th centile cutoff, only 0.7% AFR and 6.4% SAS qualified for T1D screening.

Conclusions:

WGS is a viable alternative for T1DGRS generation. This first large-scale study of WGS-based T1DGRS highlights the substantial ancestral differences in T1DGRS. This strongly advocates usage of ancestry-specific standards in clinical and research settings.

Renu Bala

University of Exeter

Poster No: 26

Understanding the relationships between type 2 diabetes and depression

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Abstract

Introduction: Major depressive disorder (MDD) and type 2 diabetes (T2D) represent two global health challenges. There is evidence of a bidirectional relationship between them, but few studies have considered the potential causal pathways. Here, we aim to investigate the causal relationship between MDD and T2D.

Methods: We used a range of Mendelian randomization (MR) methods using the most up to date GWAS summary statistic data and the UK Biobank. We assessed the bidirectional causal relationship between, a) MDD and T2D and b) MDD and glycaemic biomarkers in non-diabetic individuals.

Results: A doubling in MDD genetic liability was associated with 1.18 higher odds of T2D (95% CI: 1.14, 1.22), whilst a doubling in T2D genetic liability was associated with 1.02 higher odds of MDD (95% CI: 1.01, 1.03). Effect estimates were generally consistent in the UK Biobank when stratifying by sex and MDD was predictive of T2D in diverse ancestries. Using clusters of genetic variants suggested the causal effect of T2D on MDD was driven via body fat and obesity-mediated insulin resistance pathways. Genetic liability to MDD was also associated with higher fasting glucose and HbA1c levels in individuals without T2D.

Interpretation: We provide strong evidence of a bidirectional causal relationship between MDD and T2D, with further evidence that MDD predicts poor glycaemic control in individuals without T2D. This adds to the evidence base that MDD drives poor health habits, increasing the risk of T2D. T2D also predicts MDD highlighting the need for further research to understand this complex relationship.

Aparajita Sriram

University of Exeter

Poster No :27

RFX6, *NEUROD1*, *PDX1* cause low penetrance MODY, and truncating *INS* variants are a novel cause

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Introduction:

Previously reported MODY genes lack crucial gene-level evidence of causality, where rare variants show enrichment in a MODY cohort compared to controls. We aimed to use gene burden testing in MODY patients to assess association of 6 MODY genes with moderate/unclear evidence of causality.

Methods:

We performed rare variant (MAF<0.0001) burden testing of missense and protein-truncating-variants (PTV) in *APPL1*, *NEUROD1*, *INS*, *PDX1*, *RFX6* and *WFS1* in 2,413 Europeans with suspected MODY and 155,501 population controls with WGS from UKBioBank. We used *HNF1A* as a positive control and synonymous variants as negative controls. We replicated our results using a second independent cohort (GnomADv3, n=34,029). We used $p<0.002(=0.05/21)$ as our significance threshold.

Results:

We did not observe synonymous variant enrichment in the MODY cohort for all 7 genes ($p\geq0.05$).

We observed rare PTVs enrichment in *RFX6, PDX1, NEUROD1* in the MODY cohort but with lower odds ratios (7.7, $P<10^{-10}$, 19.3, $P<10^{-4}$ and 19.6, $P<10^{-7}$ respectively) than *HNF1A* (319, $P<10^{-65}$).

An analysis of last-exon truncating-variants identified enrichment for *INS* ($P<10^{-6}$), *HNF1A* and *PDX1* ($p<0.001$).

In contrast, we observed rare missense enrichment above significance threshold only in *INS* (4.8, $P<10^{-5}$) and *HNF1A* (6.9, $P<10^{-40}$).

Both rare PTVs and missense in *WFS1* and *APPL1* were not enriched. All results were replicated using GnomADv3 controls.

Interpretation:

WFS1 and *APPL1* variants are not associated with MODY, whereas variants in *RFX6*, *PDX1*, *NEUROD1 and INS* cause low penetrance MODY. Last exon truncating variants in *INS* are a novel cause of MODY.

Susan Martin

University of Exeter

Poster No: 28

Lower HbA1c levels in individuals with G6PD deficiency has implications for type 2 diabetes diagnosis

Susan Martin, Alys M. Ridsdale, Ji Chen, Katherine G. Young, Harry D. Green, Robin N. Beaumont, Andrew R. Wood, Trevelyan J. McKinley and Inês Barroso

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Glucose-6-phosphate dehydrogenase (G6PD) deficiency is an X-linked genetic disorder that affects red blood cells, potentially causing haemolytic anaemia. The *G6PD* variants rs1050828 and rs5030868 are known to be associated with reduced glycated haemoglobin (HbA1c) independently of glycaemia. We aimed to determine the prevalence of these variants in the UK, and test whether carriers are diagnosed with type 2 diabetes (T2D) later and develop more diabetes-related complications.

We extracted whole-exome sequencing data for *G6PD* variants rs1050828 and rs5030868 in >500,000 UK Biobank participants, and identified diagnoses of G6PD deficiency and/or haemolytic anaemia. For carriers and non-carriers, we compared HbA1c and random glucose (RG) after excluding individuals with diabetes, and age at T2D diagnosis.

The rs1050828-T allele was most prevalent in Black individuals (15%), with rs5030868-A most common in Asians (1.5%). Despite this, 92% of Blacks are not diagnosed with G6PD deficiency or haemolytic anaemia. HbA1c was on average 10.0mmol/mol [95% CI: 9.2, 10.7] lower in rs1050828-T Black male carriers compared to non-carriers, and 4.5mmol/mol [4.0, 4.9] in women. No clinical difference was observed in RG. Results for rs5030868-A in Asians were broadly similar. Male carriers of either variant were on average diagnosed with T2D 7.12 years [1.59, 12.65] later than non-carriers. Analysis for diabetes complications is currently ongoing.

Despite *G6PD* variants being common in British Black and Asian groups, the majority of carriers have no diagnosis. This may lead to delayed T2D diagnosis with increased chance of diabetes complications, potentially increasing existing health inequalities in these ethnic groups.

Dania Mendez

German Diabetes Center (DDZ) Leibniz Center for Diabetes Research

Poster No: 29

Dania Mendez*, Kálmán Bódis*, Maria Bombrich, Katsyarina Prystupa, Irina Yurchenko, Martin Schön, Clara Möser, Oana-Patricia Zaharia, Dominik Pesta, Martin Heni, Kalliopi Pafili, Yuliya Kupriyanova, Vera Schrauwen-Hinderling, Hadi Al Hasani, Michael Roden, Birgit Knebel*, Robert Wagner*

*equal contribution

The metabolic phenome of the hepatoprotective HSD17B13 splice variant rs72613567:TA suggests higher lactate clearance

Introduction & Objective: A common (~25%) splice variant rs72613567:TA in hydroxysteroid dehydrogenase 17-beta 13 (HSD17B13) was shown to reduce the risk of hepatic fibrosis and cirrhosis. The mechanism underlying the protective function remains unclear.

Methods: Carriers (n=647 of 1353) of the splice variant in the cohort of the German Diabetes Study (GDS) were identified by reverse transcription-polymerase chain reaction. Phenotyping comprised hepatic lipid content (HLC) and liver energy metabolism (inorganic phosphate (Pi), γATP by 1H/31P-magnetic resonance spectroscopy), insulin secretion, hepatic and whole-body insulin sensitivity (Botnia clamps with [6,6-^{2}H2]glucose), physical fitness (spiroergometry with lactate assessment), resting energy expenditure during fasting and clamp (indirect calorimetry) including up to 2331 measurements and covering repeated visits over 15 years.

Results: Compared to non-carriers, carriers of the hepatoprotective minor allele showed similar hepatic insulin sensitivity and γATP, but higher HLC and Pi, lower alanine aminotransferase (ALT) levels and an attenuated lactate increase after reaching the anaerobic threshold (VO2AT) (pinteraction=2E-11). This genetic modification associates with post-exercise lactate rise and was driven by elevated fasting plasma glucose levels (pinteraction=5E-4). Fasting endogenous glucose production, insulinemia, glycemia, energy expenditure, insulin sensitivity (M-value) and secretion were similar between groups. Only female carriers showed lower physical fitness (VO2 peak and VO2AT).

Interpretation: Higher hepatic Pi suggests alterations of hepatic energy metabolism in carriers of the hepatoprotective variant. The blunted increase in lactate post VO2AT, depending on fasting glucose levels, highlights a potential link between the HSD17B13 variant and altered lactate kinetics during anaerobic exercise in diabetes.

Christine Bellanné-Chantelot

Université de Paris, Hôpital Cochin, Paris

Poster No: 30

Non-invasive prenatal determination of fetal genotype in women with GCK-MODY diabetes

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Introduction. Hyperglycemia associated with GCK-MODY is moderate, and no antidiabetic treatment is required outside of pregnancy. The specificity of GCK-MODY is that the need for treatment of maternal hyperglycemia during pregnancy depends on the fetal *GCK* genotype. If the fetus has inherited the maternal *GCK* variant, its growth is normal, and therefore, treating maternal hyperglycemia is unnecessary. Conversely, if the fetus has not inherited the maternal *GCK* variant, fetal insulin secretion is increased in response to maternal hyperglycemia, increasing the risk of macrosomia by 40%. To date, non-invasive prenatal diagnosis (NIPD) for GCK-MODY is not available in routine practice.
Methods. We developed an approach based on gene panel sequencing including *GCK* and SNPs located ± 2 Mb from *GCK* and analysis of maternal haplotype imbalance in plasmatic DNA using the enhanced relative haplotype dosage method.
Results. 24 GCK-MODY women were first analyzed. Plasma DNA was extracted at 16 weeks of gestation [12-25]. The approach was conclusive in 91.7% (22/24) of cases. The test predicted 6 fetuses carrying the maternal risk haplotype among the 22 conclusive cases. Comparison of these results with the child's genotype at birth showed a concordance rate of 100%. A replication study on 17 samples using the same approach and aiming to compare two statistical analyses is currently underway.
Conclusion. This study demonstrates the feasibility of NIPD for GCK-MODY. The expected benefit is to tailor the therapeutic management of pregnancy based on knowledge of the fetal genotype, thus avoiding unwarranted insulin treatment in 50% of women with GCK-MODY.

Cécile Saint Martin

Department of Medical Genetics, Sorbonne University

Poster No: 31

Variants altering an intronic regulatory element of *HK1* are responsible for congenital hyperinsulinism.

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Introduction

Congenital hyperinsulinism (CHI) is characterized by inappropriate insulin secretion in pancreatic beta cells leading to hypoglycemia of varying severity. Non-coding variants within a hexokinase 1 (HK1) regulatory element were recently shown to lead to hyperinsulinism *via* the alteration of transcription factor binding sites and the resulting abnormal expression of HK1. This study aimed to investigate the phenotypic variability of HK1-related CHI and to evaluate whether the observed differences could be explained by the location of the variant.

Methods

We analyzed by sequencing and quantitative PCR a regulatory region of *HK1* in 489 CHI subjects previously screened for the main CHI genes. The cohort included 82 cases (17%) with severe forms unresponsive to diazoxide treatment.

Results

We identified variants in 70 individuals from 34 families. While the *HK1* variants detected in the 5 probands with unresponsive CHI mostly occurred *de novo*, the segregation study of the variants identified in the 29 probands with moderate forms demonstrated incomplete penetrance and phenotypic variability.

Eleven different molecular abnormalities (9 SNVs, 1 indel and the complete deletion of the region) were highlighted. Six of them affected a transcription factor binding site. Four of the 5 probands with unresponsive forms presented a variant affecting all three NKX2-2, NFAT and FOX binding sites. The last patient carried the deletion of a single base in the NFAT domain.

Interpretation

This study suggested a correlation between the extent of the alteration of the regulatory elements of *HK1* and the phenotypic diversity observed between cases with *HK1*-CHI.

Cécile Saint Martin

Department of Medical Genetics, Sorbonne University

Poster No: 32

Functional validation of spliceogenic *HNF1B* variants *via* the analysis of transcripts from blood samples

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Introduction

When the application of international classification rules fails to allow reporting variants as pathogenic it is of utmost importance to have access to data on proteins or transcripts bearing these variants of unknown significance. This functional insight is impeded by the limited access to the relevant tissue as many genes of interest have restricted tissue- and/or time-dependent expression. In the case of monogenic diabetes, most genes have been shown to have limited or no expression in blood, the most readily accessible tissue.

Methods

Two potential spliceogenic *HNF1B* variants, based on SpliceAI predictions, were identified in patients displaying phenotypes consistent with the HNF1B-syndrome, c.544+4A>C and c.808A>C, p.(Arg270=). Blood samples were collected on PaxGene Blood RNA Tubes. RNA was extracted and RT-PCR was performed. Amplicons were Sanger-sequenced.

Results

The analysis of the sequences from the transcripts extracted from blood demonstrated, in addition to the wild-type transcript, for c.544+4A>C a shift of the donor splice site 32bp upstream of the canonic site and, for c.808A>C, the activation of an intronic cryptic splice site resulting in the retention of 29 intronic base pairs. Both variants result in transcripts with premature termination codons.

Interpretation

Our study revealed the unexpected presence of *HNF1B* transcripts in blood and demonstrated *in vivo* the impact of these variants. It ultimately determined that these variants were probably pathogenic.

Most importantly this analysis proved that a splice pattern was obtainable on blood even for genes listed in databases as not expressed in this tissue.

Cécile Saint Martin

Department of Medical Genetics, Sorbonne University

Poster No: 33

Digenic diabetes in a pedigree with *GCK* and *ABCC8* dominant variants

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Introduction

Monogenic diabetes is a phenotypically and genetically heterogeneous disease. It encompasses moderate hyperglycemia caused by variants of *GCK* as well as the more complicated phenotypes caused by alterations of *ABCC8*. A few variants of the latter can for example be responsible both for adult diabetes and for the hyperinsulinemic phenotype in neonates. Establishing a genetic diagnosis of diabetes is therefore challenging, not mentioning the added complexity introduced by type 2 diabetes risk factors.

Methods

A panel of genes involved in monogenic diabetes was analyzed in a multiplex family displaying highly variable phenotypes. Segregation analysis was subsequently conducted by Sanger sequencing and quantitative PCR. Functional validation of the *ABCC8* variant was performed *via* Western Blot, Rb^+ efflux, and inside-out patch-clamp recording.

Results

Three sibs were described with a diagnosis of diabetes between 8 and 15 years old and a family history of type 2 diabetes. They all carried a maternally inherited *ABCC8* missense variant, two of them together with the paternal large deletion of *GCK*. One child only inherited the *ABCC8* variant and developed hyperinsulinism. Biochemical studies demonstrated loss of function of the *ABCC8* variant. Her sister who had inherited both *ABCC8* and *GCK* variants did not show any glycemic anomaly suggesting compensatory effects.

Interpretation

The presence of either one or two monogenic variants together with type 2 risk factors probably explain the variable clinical expressivity of diabetes within a single family both at diagnosis and during evolution. This should be considered when families display heterogeneous phenotypes.

Manonanthini Thangam

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Poster No: 34

Title: Diabetes endotypes, physical activity and early adulthood strength and endurance

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Introduction: Regular physical activity enhances glucose sensitivity and decreases risk of type 2 diabetes. Here, we evaluate association between diabetes endotypes with different clinical characteristics, physical fitness at age 18, and genetic estimates of fitness and activity, to better understand the role of these factors in development of diabetes.

Methods: We analyzed association between polygenic scores (PGS) and diabetes endotypes in the ANDIS-MDC cohort, including 6,877 diabetes cases and 2,679 diabetes free controls. Physical fitness parameters at age 18 were obtained for 4,373 male ANDIS participants and 235,953 population controls from the Swedish Military Conscription Registry.

Results: At age 18, BMI was already highest in individuals who would later develop moderate obesity-related diabetes (MOD, mean 24.5±4.0), but also higher in the severe insulin-deficient diabetes (SIDD, 22.3±3.4) and severe insulin-resistant diabetes (SIRD, 22.4±3.3) compared to controls (21.6±2.8), whereas the mild age-related diabetes (MARD) group was leaner (21.0±2.3). SIRD had the lowest aerobic capacity (-5.6%) and BMI-adjusted grip strength and the strongest association with PGS for grip strength and self-reported physical activity. PGSs for moderate to vigorous physical activity were negatively associated with all groups except MARD. Leisure screen time was positively associated with all groups with the largest effect in MOD and SIRD.

Interpretation: Diabetes endotypes show different associations with physical activity and capacity already in early age, 30-50 years before diagnosis, with the largest effects observed for individuals who will develop insulin-resistant diabetes (SIRD). Further investigation is required to disentangle the relationship between these phenotypes and other life-style factors.

Juliette A de Klerk

Leiden University Medical Center, the Netherlands

Poster No: 35

Small non-coding RNAs in plasma are associated with type 2 diabetes subgroups

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ABSTRACT

INTRODUCTION

Type 2 diabetes (T2D) is a heterogeneous disease with varying risks of rapid progression. Grouping individuals into five established clusters based on individual characteristics may aid to the identification of those prone to rapid progression. We have shown before that characteristics of the clusters are also reflected in multi-omics signatures. However, whether this is also reflected in plasma small non-coding RNAs (sncRNAs) expression is unknown. This study aims to uncover differences in sncRNAs in individuals with T2D categorized into five clusters.

METHODS

In the Hoorn Diabetes Care System (DCS) cohort, participants were clustered by age, BMI, HbA1c, C-peptide, and HDL-cholesterol, yielding the SIDD, SIRD, MOD, MD and MDH clusters (n=412). Utilizing plasma sncRNA-seq, we identify distinct cluster-specific sncRNAs. To elucidate their potential functions, we examined tissue expression, identified targets using miRDB, conducted gene set enrichment analyses on the targets through Reactome and examined correlations with plasma protein expression.

RESULTS

The insulin resistant cluster (SIRD) exhibited aberrant expression of thirteen sncRNAs, while the high BMI cluster (MOD) featured ten differentially expressed sncRNAs. sncRNAs in the MOD cluster were predominantly expressed in the liver, with strong correlations among the upregulated sncRNAs. Conversely, sncRNAs differentially expressed in the SIRD cluster demonstrated expression in various tissues, and their predicted targets exhibited enrichment for the TGF-beta signaling pathway. Plasma proteome analysis confirmed this association.

CONCLUSIONS

We observed differential expression of sncRNAs among type 2 diabetes clusters. Our observations could deepen our understanding of molecular mechanisms, unveiling potential differences in development, progression, and risk factors for each cluster.

Rasmus Tanderup Jensen

University of Copenhagen - Novo Nordisk Foundation Center for Basic Metabolic Research

Poster No: 36

Inflammatory Marker Dynamics Following Bariatric Surgery: A 3 and 12-Month Longitudinal Analysis

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Introduction

Overweight and obesity increase cardiometabolic morbidity and mortality, which may be attributable to systemic low-grade inflammation but more knowledge, is needed on how weight loss following bariatric surgery changes the systemic inflammation and furthermore whether the surgical procedure has impact hereon. In this study, we assessed the changes in plasma levels of cytokines, chemokines and cytokine receptors in individuals with obesity three and twelve months after bariatric surgery.

Methods

We included seventy individuals with obesity referred for bariatric surgery. Thirty individuals underwent Roux-en-Y Gastric Bypass (RYGB) and forty sleeve gastrectomy (SG). Fasting project blood samples were carried out at baseline (before surgery) and three and twelve months after surgery. Eleven healthy persons served as controls. Plasma cytokine expression was measured by Olink 96 Target inflammation plate. A linear mixed model was used to assess differences in inflammatory markers between time points and groups.

Results

At baseline, 36 cytokines were substantial increased between bariatric patients and healthy controls. 13 and 27 cytokines were significantly decreased at three and twelve months after bariatric surgery, respectively, compared to the baseline while two cytokines (CCL25 and CCL28) were significantly increased after twelve months. Only one cytokine (CCL25) displayed interaction with the surgery type.

Interpretation

The increased expression of systemic inflammatory cytokines is mostly reversed by bariatric surgery. The surgical procedure, RYGB or SG had no impact on this.

Annika Sem Sippel Krill

University of Bergen

Poster No: 37

Single-nucleotide editing for translating GWAS signals into new molecular mechanisms and treatment targets

Authors: Annika S. Krill[1], M.Sc., Nina T. Samuelsen[1], M.Sc., Shanima Shanu Mirza [1], M.Sc., Ingrid J. Petersen[1], B.Sc., Tiffany C. K. Ngan[1], B.Sc., Jan-Inge Bjune[1], Ph.D., Gunnar Mellgren[1], M.D., Ph.D., Melina Claussnitzer[2], Ph.D., Simon N. Dankel[1], Ph.D..
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Introduction:

Increased visceral fat, independent of BMI, is a risk factor for T2D, but the underlying genetics are largely unknown. A recent GWAS identified a novel genomic risk locus (11q23.3) for visceral adiposity and T2D, but the associated SNPs are non-coding, impeding biological interpretation.

Methods:

Towards uncovering the mechanisms involved, SNPs in high LD with the tag-SNP at 11q23.3 were identified using HaploReg, and ENCODE epigenetic data was interrogated to predict cell types with associated active enhancers. To experimentally validate the predicted enhancer regions, DNA segments were cloned from patients with risk vs protective haplotype and analyzed *in vitro* by luciferase reporter assays in cultured preadipocytes. In segments with genotype-dependent enhancer activity, SNPs were mutated individually *in vitro* to assess causality. Upstream mediators were inferred via TF-binding predictions.

Results:

We have identified five candidate causal SNPs that likely act in adipose-derived mesenchymal stem cells (ASCs). Among these, rs1799993 is situated in the binding site of the RARB repressor of visceral adipogenesis, and is predicted to disrupt its binding in risk-carriers. Genomic and epigenetic editing of the predicted causal SNPs, followed by RNA-seq, is being performed in ASCs to validate the causal SNPs and identify downstream target genes.

Interpretation:

We have applied a variant-to-function approach to investigate the mechanisms underlying the 11q23.3 risk locus for visceral adiposity. Identifying likely causal SNPs has enabled prediction of upstream mechanisms related to retinol signaling. Further experiments will determine whether risk carriers of rs1799993 exhibit increased visceral adipogenesis due to disruptions in this signaling pathway.

Bhargav Ganesh Naveen

University of Exeter

Poster No: 38

Clustering of fetal birth weight-associated loci reveals glycemic, placental and infant growth pathways

Authors:

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Introduction:
Genetic variants associated with birth weight (BW) are variably associated with adult anthropometric traits and type 2 diabetes (T2D) susceptibility, contributing to epidemiological relationships between these temporally-distinct traits. To improve understanding of pathways linking fetal growth with glycemic traits and later growth, we (i) clustered BW-associated loci based on multiple variant-trait associations, and (ii) investigated associations between clusters and early-life characteristics in a UK cohort.

Method:
We selected 179 lead variants from fetal GWAS of BW (minor allele frequency>0.01; stringent LD-pruning) and looked-up their associations in GWAS of 11 neonatal, adult anthropometric and adult glycemic traits. We applied non-negative matrix factorization to cluster variants. We calculated genetic scores (GS) for each cluster and tested associations with cord insulin and anthropometric traits at birth, 12wks, 1yr and 2yrs in upto 706 individuals from the EFSOCH study.

Results:
We successfully grouped 50 variants into 4 clusters, indicating mechanisms related to higher (1)placental weight, (2)birth length, (3)adult height and (4)reduced T2D risk. There were no associations between any cluster-specific GS and cord insulin. Clusters 1, 2 and 3 showed associations ($p<0.05$) with birth anthropometric traits, but only cluster 3 was consistently associated with anthropometric measurements from birth to 2 years.

Interpretation:
Genetic variants underlying BW may be partitioned into those with only fetal effects vs. those with fetal and adult effects. Only variants from the “adult height” cluster were associated with infant growth, and these were distinct from variants influencing later T2D risk. Larger studies are necessary to investigate differential effects on cord insulin levels or adiposity.

Evelina Stankevic

University of Copenhagen, Novo Nordisk Foundation Center for Basic Metabolic

Poster No: 39

Genome-wide association study of dental caries and correlations with cardiometabolic traits

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Introduction: Recent studies indicate a potential link between dental caries (DC) and cardiometabolic diseases, suggesting that shared genetic factors may play a role in influencing the development and progression of both conditions. Our objective was to map the genetic variations associated with DC and investigate the shared genetic influences between DC and cardiometabolic diseases.

Methods: We conducted a genome-wide association study of objectively measured childhood DC in permanent dentition in 72,139 individuals from the Danish Blood Donor Study Cohort. We used LD score regression to examine genetic correlations across cardiometabolic, oral, psychiatric and lifestyle traits. We performed fine-mapping to pinpoint causal variants, followed by colocalization to determine overlapping genetic signals between DC and correlated traits.

Results: We found eight genetic loci associated with DC ($P < 5 \times 10^{-8}$), six of which were previously unreported. Genetic correlations were identified between DC and several cardiometabolic traits, including type 2 diabetes ($R_g = 0.27$, $P = 3.4 \times 10^{-8}$), body mass index ($R_g = 0.24$, $P = 1.0 \times 10^{-7}$), coronary artery disease (CAD, $R_g = 0.18$, $P = 1.7 \times 10^{-4}$) and high-density lipoprotein (HDL, $R_g = -0.26$, $P = 3.1 \times 10^{-7}$). Colocalization suggested functional links between DC and CAD (a locus on chromosome 3 with PP.H4 = 0.97*)*, and HDL (loci on chromosomes 4 and 22 with PP.H4 > 0.92*)*.

Interpretation: We highlight the polygenic nature of DC and through identified genetic correlations and colocalization patterns suggest shared pathophysiological mechanisms between DC and cardiometabolic traits.

Martin Schön

Heinrich-Heine University in Düsseldorf

Poster No: 40

Combining next-generation sequencing and metabolic phenotyping to elucidate reduced mitochondrial respiration in type 2 diabetes

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*equal contribution

Introduction: Recent advances in RNA Sequencing techniques by identifying tissue-specific alternative splicing showed a potential to provide new insights in molecular mechanisms underlying pathophysiological changes of energy metabolism. For example, full-length transcriptomics based on single molecule real-time sequencing (SMRT-Seq) allows precise detection of isoforms with 99% accuracy in an unbiased approach. We aimed to apply SMRT-Seq in human skeletal muscle, and in a combination with comprehensive metabolic phenotyping to elucidate mechanisms of reduced mitochondrial respiration in type 2 diabetes (T2D).

Methods: Muscle biopsies were taken from 9 humans with T2D as well as 9 age- and body mass index-matched glucose tolerant men (CON). Whole-body insulin sensitivity (WBIS) was assessed by hyperinsulinemic-euglycemic clamps and muscle mitochondrial respiration by high-resolution respirometry.

Results: Metabolic phenotyping revealed reduced WBIS, fatty acid-driven, complex I and complex II muscle mitochondrial respiration in T2D compared to CON. SMRT-Seq identified in total ~14 000 unique genes with ~ 67 000 unique isoforms in human skeletal muscle, and detected 4 splicing variants of a gene encoding F1 subunit α ATP Synthase (ATP5F1A). Based on comparative transcriptomics, the expression in muscle of CON was higher than in people with T2D, and two of the novel transcripts were present only in CON.

Interpretation: In the present study, employing SMRT-Seq identified splicing variants of ATP synthase which differentiated people with T2D with controls. In turn, understanding the mechanisms of altered mitochondrial respiration can help to identify novel therapeutic targets in T2D.

Karianne Fjeld

University of Bergen

Poster No: 41

How to find new cases of CEL-MODY: check the *CEL* VNTR sequence!

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ABSTRACT

Introduction: Pathogenic variants in the carboxyl ester lipase gene (*CEL*) cause CEL-MODY (MODY8). CEL is a digestive enzyme produced by the exocrine pancreas, and CEL-MODY is the only MODY type in which the mutated gene is not expressed in the islets. After the initial discovery of two Norwegian CEL-MODY families in 2006, only three pedigrees have been published with convincing data substantiating the diagnosis. The MODY-causing *CEL* variants are single-base deletions within a complex VNTR, which implies that the pathogenic variants often are filtered away in NGS-based diagnostics. To find additional CEL-MODY cases, we investigated MODY cohorts from Norway, Finland and UK.

Methods: The *CEL* VNTR sequence was scrutinized in probands who had undergone screening by NGS without genetic findings. Suspected single-base deletions in the VNTR were verified by Sanger sequencing and clinical information/family history recorded.

Results: One Norwegian and one Finnish family were identified with a single-base deletion in *CEL* VNTR repeat 4 and repeat 2, respectively. Thus, CEL-MODY now comprises 3/452 (0.7%) of probands diagnosed with monogenic diabetes in the Norwegian MODY Registry and 1/124 (0.8%) in the FINNMODY study. Moreover, one proband with a deletion in *CEL* VNTR repeat 4 was found among recently screened MODY cases from UK. The probands' medical records revealed autosomal dominantly inherited diabetes, low fecal elastase, and signs of exocrine dysfunction.

Interpretation: To identify new cases of CEL-MODY, the *CEL* VNTR needs special attention in patients screened by NGS approaches. A fecal elastase test may aid the diagnosis. CEL-MODY is more frequent than previous data suggest.

Ethan de Villiers

University of Exeter

Poster No: 42

Title: Investigating the causal link between prolonged hyperglycaemia and hospitalisation for infection: a Mendelian randomisation study

Authors: Ethan de Villiers, Rhian Hopkins, Michael N. Weedon, John M. Dennis, Harry D. Green

Introduction
Recent research has causally implicated prolonged elevated glycaemia in the development of multiple conditions, such as frozen shoulder and diabetic foot. We have therefore used similar genetic methodologies to investigate a potential causal link between prolonged hyperglycaemia and hospitalisation for different types of infections.

Methods
UK Biobank participants were classified into 4 groups: those with a record of hospitalisation for a bacterial (N=49,675) or fungal infection (N=819), or influenza (N=1,041), and a control group of participants with no record of a hospitalisation for infection (N=448,893). For each infection type, a Mendelian randomisation (MR) analysis was conducted to test for a causal link between HbA1c on infection outcomes.

Results
All infection groups had a significantly ($p<10^{-16}$) increased BMI, HbA1c, waist-hip-ratio and diabetes prevalence compared to controls. The effect sizes were similar across groups, but highest in participants with multiple infections. Distributions of glycaemic and non-glycaemic genetic risk scores were similar across all infection groups and controls. Furthermore, using MR we found no significant evidence that prolonged elevated glycaemia causally influenced bacterial, fungal, or influenza hospitalisations (p-values=0.469, 0.461, 0.527).

Interpretation
Using well-powered MR, our study found no evidence that prolonged elevated glycaemia played a causal role in increasing the risk of bacterial, fungal or influenza infection hospitalisations. Further research is required to understand why people with diabetes are at an increased risk of infections-based hospitalisation.

Rachel Anand Nethala

University of Bergen

Poster No: 43

A structural approach to study *HNF1B* variants and their implication in health and disease

Rachel A. Nethala[1], Aishwarya Pavithram[1], Laura Kind[1,4], Martin S. Berge[1], Monika Ringdal[1], Thomas Arnesen[4], Janne Molnes[1,2], Bente B. Johansson[1], and Pål R. Njølstad[1,3]

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Introduction HNF-1B is a transcription factor, crucial to the development of the kidneys, genitourinary tract, liver, lungs, gut, and the pancreas. Certain variants in *HNF1B* encoding the protein are causative of MODY. HNF-1B is comprised of three functional domains, the N-terminal dimerization domain (DD) and the bipartite DNA-binding domain (DBD), followed by a transactivation domain (TAD) at the C-terminal end. While the functional properties of HNF-1B have been extensively studied, information on its structural features is limited. Therefore, our aim is to investigate wild type and mutated HNF-1B structure and their interactions with DNA and proteins to provide knowledge on the mechanism of its function in health and disease.
Methods The Gateway cloning method was employed to generate constructs (full-length HNF-1B, DD, DBD, DD-DBD, TAD, QSP/exon 7), later transformed into *Rosetta* cells. Expression conditions for DD-DBD were optimized, followed by large-scale expression and subsequent purification by Ni-NTA and size-exclusion chromatography. Proteins will be characterized using circular dichroism (CD) and isothermal titration calorimetry (ITC) to examine protein secondary structure, folding, binding affinity, stoichiometry, and thermodynamics. Further, HNF1B-MODY variants will be generated and characterized similarly to analyze their structural effects.
Results We have optimized expression conditions for DD-DBD (37°C for 3 hours) and DBD (20°C for 20 hours) proteins. The DD-DBD protein has been expressed in large-scale and purified.
Interpretation We aim to structurally characterize the full-length HNF-1B, starting with the DD-DBD domains. Studying HNF1B-MODY variants within specific domains can provide insight into their structural and mechanistic consequences on protein function.

Satoshi Tanaka

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Poster No: 44

Authors: Satoshi Tanaka[1,3], Hiroyuki Akagawa[1], Naoko Iwasaki[2,3]

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Systematic Genetic Analysis achieved 57.1% of detection rate in Japanese MODY patient.

Introduction: Maturity-Onset Diabetes of the Young (MODY) is a diabetes mellitus subtype caused by single genes. The detection rate of the responsible gene is reported to be 27% in the United Kingdom, indicating that the causative gene remains unknown in three-quarters of clinically diagnosed MODY cases. To improve the detection rate, we applied a comprehensive genetic testing using whole exome sequencing (WES) followed by Multiplex Ligation-dependent Probe Amplification (MLPA) and functional analyses.

Methods: A cohort of 21 participants recruited from the Tokyo Women's Medical University Diabetes Center from April 2020 to March 2022, who met the following clinical criteria of MODY was investigated. WES was performed first, followed by MLPA analysis for participants who were negative on the basis of WES. Undetermined variants were analyzed according to their functional properties.

Results: WES identified 7 pathogenic variants; 3 in *HNF1A* (c.327-1G>A, p.Gln176Ter, p.Arg131Trp), 1 each in *HNF4A* (p.Arg112Gln), *GCK* (p.Cys382Ter), *ABCC8* (p.Gly1478Arg), and *WFS1* (p.Asn746Lysfs*13). We also identified 3 novel likely pathogenic variants in *GCK*(p.Asp363Gly, p.Ser445Arg), *PDX1* (p.Glu145Lys), functional analyses revealed that 1 in 3 variants was pathogenic. MLPA analysis applied to the remaining 13 undetermined samples identified 4 cases with pathogenic CNVs, 3 in *HNF4A* and 1 in *HNF1B*.

Interpretation: Pathogenic variants were identified in 12 participants (12/21, 57.1%) – the highest rate reported to date. Notably, one-third of the participants had CNVs in *HNF4A* or *HNF1B*, indicating a limitation of WES-only screening.

Leen 't Hart

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Poster No: 45

Circulating small non-coding RNAs associate with kidney function in people with type 2 diabetes

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Abstract

Introduction Micro- and macrovascular complications are common among persons with type 2 diabetes. Recently there has been growing interest to investigate the potential of circulating small non-coding RNAs (sncRNAs) as biomarkers and drivers of the development of diabetic complications. In this study we investigate to what extent circulating sncRNAs levels associate with prevalent diabetic kidney disease (DKD) in persons with type 2 diabetes.

Methods Plasma sncRNAs levels were determined using sRNA-seq, allowing detection of miRNAs, snoRNAs, piRNAs, tRNA-fragments and various other sRNA classes. We tested for differentially expressed sncRNAs in persons with type 2 diabetes, with DKD (n=69) or without DKD (n=405). In secondary analyses, we also tested the association with eGFR, albuminuria (UACR) and the plasma proteome.

Results In total seven sncRNAs were significantly associated with prevalent DKD ($P_{FDR} \leq 0.05$). Although miRNAs represent the majority of the sncRNAs measured (64%) only one miRNA was significantly associated while the majority of the significant sRNA belonged to the snoRNA class (71%). Similar results were observed for eGFR and UACR. High expression of these circulating sncRNAs in tissues other than kidney suggest a role in inter-organ communication. In addition, the seven sncRNAs, and especially piR-019825, were associated with plasma levels of 80 proteins of which several have known associations with kidney function.

Interpretation Small ncRNAs present in the circulation associate with DKD in persons with type 2 diabetes. Further studies are warranted to explore their biomarker potential and elucidate the biological role of sncRNA in DKD and in particular snoRNAs and piR-019825.

Aishwarya Pavithram

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Poster No: 46

Functional analyses of *HNF1B* variants identified in a French cohort: advancing personalized medicine in diabetes

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Introduction

Pathogenic variants in the *HNF1B* gene result in HNF1B-MODY, a syndrome including diabetes with renal abnormalities. Upon genetic testing for monogenic diabetes, many single nucleotide variants (SNV) of *HNF1B* have been identified, most of them being private. Limited scientific information or conflicting data challenge the ability to classify these variants, hence, they often end up in the category "variants of unknown significance (VUS)". Functional analyses may aid the interpretation process, and development of tools for the functional evaluation of these variants is therefore critical.

Methods

Patients recruited through MODY diagnostics underwent NGS panel screening or targeted screening of monogenic diabetes genes, including *HNF1B*. 31 rare *HNF1B* VUS were evaluated by functional analyses in HeLa cells devoid of endogenous *HNF1B* expression. We examined the variant proteins' ability to bind to the Rat Albumin promoter and transactivate the target gene using gel-shift and luciferase reporter assays.

Results

Eight variants; p.L12F, p.M129V, p.R233H, p.R235W, p.R235Q, p.R235L, p.R261G, and p.N289D exhibited substantial reductions in both transactivation (≤ 50%) and DNA-binding (≤ 55%) capacities, 13 variants displayed normal transactivation function (≥ 90%) compared to the wild type (100%). The rest remained VUS due to limited information and/or conflicting data. Integration of functional data with clinical phenotype, family and segregation information, international collaboration (MDEP), GnomAD allele frequency, and bioinformatics enabled the classification of functionally defective variants as (likely) pathogenic.

Interpretation

Our study emphasizes the importance of conducting functional tests on missense variants to accurately interpret variant pathogenic effects. This approach allows correct diagnosis, improving patient care.

Pamela Bowman

University of Exeter

Poster No: 47

Early sulphonylurea treatment improves non-verbal IQ in *KCNJ11*-related iDEND (developmental delay, epilepsy and neonatal diabetes)

AUTHORS

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ABSTRACT (250 words)

INTRODUCTION

Central nervous system (CNS) features in individuals with iDEND (intermediate developmental delay, epilepsy and neonatal diabetes) due to *KCNJ11* mutations may show partial improvement with sulphonylurea treatment, likely due to a direct effect of sulphonylureas on brain K_{ATP} channels. The incomplete CNS response to sulphonylureas contrasts with the excellent beta-cell response. This may relate to the age of initiation of sulphonylureas, with earlier treatment restoring brain K_{ATP} channel function during critical periods of neurodevelopment. We aimed to assess the impact of timing of sulphonylurea initiation on cognitive outcomes in the largest group of individuals with *KCNJ11*-related iDEND due to the V59M mutation reported to date.

METHODS

We assessed 9 individuals with the *KCNJ11* V59M mutation using the Leiter-3 cognitive battery. Leiter-3 scores were converted to standard scores. Nonverbal intelligence quotient (NVIQ) was compared between individuals treated with sulphonylureas early (before 12 months of age,n=5) and late (after 12 months of age,n=4), using non-parametric statistics.

RESULTS

Individuals treated with sulphonylureas in the first year of life had higher NVIQ scores than individuals treated later (median (range) NVIQ 61 (47-70) vs 35 (30-43), p=0.02). The individual with the highest NVIQ score (70) also had sulphonylurea exposure *in utero* due to treatment of maternal diabetes.

INTERPRETATION

Our data support early genetic diagnosis and initiation of sulphonylurea treatment in individuals with *KCNJ11*-related iDEND, to improve cognitive development. Further research will investigate effects in a larger cohort, assess broader neurodevelopmental outcomes, and explore whether *in utero* sulphonylurea therapy has additional benefits for the CNS.

Delphine Bouvet

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Poster No: 48

Incidental diagnosis of recessive forms of monogenic diabetes associated with the *WFS1* gene

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Introduction
Next-generation sequencing offers the opportunity to analyze rare and syndromic forms of monogenic diabetes. It revealed that 3% of positive cases carried pathogenic variants of the *WFS1* gene, classically associated with Wolfram Syndrome (WS). This syndrome is characterized by the presence of diabetes insipidus, sensorineural deafness, bilateral optic atrophy and various neurological signs.

Methods
Clinical and molecular examination of 28 patients (14F, 14M) with *WFS1* variants.

Results
This study shows that their diabetes had early onset (median age 8,5 years [1-36]) and was mainly treated with insulin (82%). While some patients actually had ocular damage (5), deafness (5) or diabetes insipidus (2), 16/28 had no symptom reported in addition to their diabetes. Among the latter, the announcement of the molecular result was the opportunity for a re-examination of 9 files. For 5 of them (55.5%), additional elements were part of WS spectrum. Molecular results also showed the complexity of *WFS1* variants interpretation, with a majority of recessive forms (27/28) and occasionally dominant forms.

Interpretation
This study highlights the variable penetrance and expressivity associated with the *WFS1* gene, and the benefits of including syndromic monogenic diabetes etiologies in gene panels. These incidental diagnoses underline the need, when prescribing a molecular study, to anticipate a potential result that goes beyond diabetes, requiring appropriate monitoring and genetic counseling. The downside is that analyzing *WFS1* leads to the identification of numerous variants of uncertain significance, whose involvement in diabetes is not easy to demonstrate in the absence of functional studies.

Cassandra Spracklen

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Poster No: 49

Associations of Combined Genetic and Lifestyle Risks with Incident T2D in the UK Biobank

Introduction: To determine whether unhealthy lifestyle behaviors were associated with similar increases in the risk of incident T2D among individuals with low, intermediate, and high genetic risk, we performed a genetic risk score (GRS) by lifestyle interaction analysis within 460,133 individuals from the UK Biobank.

Methods: Multi-ancestry GRS were calculated by summing the effects of 1,286 T2D-associated variants (number of risk alleles multiplied by the reported effect size); low, intermediate, and high GRS were defined by tertiles of GRS. We used baseline self-reported data on smoking, BMI, physical activity, and diet to categorize participants as having an ideal, intermediate, or poor level of lifestyle factors. Cox proportional hazards regression models were used to generate adjusted hazards ratios (HR) and associated 95% confidence intervals (95% CI).

Results: During follow-up (median 8.9 years), 21,569 (4.7%) participants developed T2D. GRS (P<2e-16) and lifestyle classification (P<2e-16) were independently associated with increased risk for T2D. Compared with “ideal” lifestyle in the lowest genetic risk strata, individuals with a “poor” lifestyle had substantially increased risk for T2D in all genetic risk strata, with adjusted HR ranging from 7.5 (low genetic risk; 95% CI 5.81-9.74) to 29.5 (high genetic risk; 95% CI 23.77-36.53). Results were consistent when using ancestry-specific GRS and in analyses stratified by sex.

Interpretation: Overall, high genetic risk and poor lifestyle were the strongest risk factors for incident T2D. Individuals at all levels of genetic risk greatly mitigate their risk through their behavioral lifestyle.

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Poster No: 50

I got 99 problems: Four years with the TRANSLATE precision medicine implementation project

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Introduction

Management of common complex diseases such as diabetes is increasingly expected to involve the identification of genetic variants that can be translated into clinical care. However, implementing solutions that facilitate genomic medicine at scale remains a challenge.

Methods

The TRANSLATE project, initiated in 2020, aims to perform whole genome sequencing for the identification of rare high-impact monogenic diabetes variants, pharmacogenetic variants and polygenic risk scores for 5,500 individuals with type 2 diabetes and 1,000 individuals with gestational diabetes across five hospitals in the Capital region of Denmark.

Results

Our experiences in TRANSLATE indicate that patients are receptive to genomic precision medicine. However, clinicians express concerns about the utility and time requirements of genomic medicine and call for more education and information on how to leverage and communicate actionable genetic variation. The project has revealed legislative gaps in how data from research and clinical settings can be utilized and a lack of infrastructural readiness for movement and accessibility of comprehensive genetic data. Preliminary results from the first ~800 patients show a lower than expected rate of actionable genetic variation in monogenic diabetes genes, indicating that the impact of implementation is context dependent.

Interpretation

Overcoming the identified obstacles is essential to realizing the full potential of genomic medicine. As the TRANSLATE project continues, more projects are needed to further explore and address the challenges of precision medicine implementation. These continued efforts will play a crucial role in advancing the use of genomic medicine, ultimately leading to more effective patient care.

Petra Dusatkova

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Poster No: 51

Rare forms of (non)syndromic monogenic diabetes in the registry of patients susceptible for monogenic diabetes

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Introduction

Monogenic diabetes accounts for approximately 3.5% of patients manifesting diabetes till 30 years. Majority of these patients had subtypes of Maturity-Onset Diabetes of the Young (GCK/HNF1A/HNF4A-MODY). We aimed to describe rare forms of monogenic (non)syndromic diabetes in a Czech registry of patients susceptible for monogenic diabetes.

Methods

Probands with pathogenic variants in all pancreas-related but major MODY genes were selected. Data were obtained from the clinical questionnaires. The genetic testing was performed by Sanger sequencing, MLPA, followed by tNGS of 52 (63) genes since 2018.

Results

Out of 1903 probands with suspected monogenic diabetes, rare forms were detected in 52 families (87 persons). Median age at diabetes diagnosis was 17 (13-30) years. Median HbA1c reached 58 (45-69) mmol/mol (7.5%; 6.3-8.5%). Insulin was prevailing type of treatment (59.7%).

Gene	Persons/families	Comorbidities
HNF1B	27/21	Renal cysts (n=7), hypomagnesemia (n=8), chronic renal insufficiency (n=3), kidney transplantation (n=1), kidney anomaly (n=3), pancreas atrophy (n=2)
INS	14/7	
WFS1	8/7	Optic hypoplasia (n=3)
MT-TL1	14/6	Hearing impairment (n=8), cardiomyopathy (n=2), stroke (n=2), heart transplantation (n=1)
PDX1	8/4	
ABCC8	8/2	
INSR	2/2	
CEL	3/1	Pancreas atrophy and cysts (n=2)
KCNJ11	1/1	
RFX6	2/1	

Diabetes alone displayed 19 persons with *HNF1B, MT-TL1* or *WFS1* anomaly.

Interpretation

Rare forms of monogenic diabetes caused by variants in 10 genes accounted for 7.1% of all families with monogenic diabetes. Genetic diagnosis not only clarify the diabetes aetiology but importantly allow to specifically investigate and treat in time additional comorbidities in probands with syndromic monogenic diabetes mimicking as “diabetes only” phenotype.

Laura Saso Jiménez

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Poster No: 52

Polygenic Risk Scores partially explain undiagnosed cases in Spanish patients with suspected monogenic diabetes.

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Introduction:

Genetic testing is required to diagnose monogenic diabetes in patients with family history, young onset, and negative pancreatic autoimmunity. However, genetic screening only identifies a monogenic cause in ~60% of studied cases. The **aim** of this study was to evaluate the utility of type 1 diabetes (T1D) and type 2 diabetes (T2D) polygenic risk scores (PRSs) to clarify the disease origin in suspected monogenic diabetes (MODY) patients negative for genetic studies.

Methods:

The study included Spanish patients (n=572) with suspected MODY, studied previously with Next-Generation-Sequencing panels. All cases were genotyped with the *Illumina Infinium Global-Screening-Array*. After quality control and imputation, we applied previously developed PRSs to determine T1D and T2D polygenic risk. We used multivariate generalized linear models to test the association between the PRSs, in cases with confirmed MODY vs patients without pathogenic variants in analyzed MODY genes (MODYx group).

Results:

The 90th percentile of the T1D-PRS was associated with an odds-ratio of being MODYx of 6.14 (1.68-21.62, 95% CI, p=0.0047) and the 90th percentile of the T2D-PRS with an odds-ratio of being MODYx of 3.62 (2.02-6.50, 95% CI, $p=1.51x10^{-5}$), both compared to confirmed MODY. A model combining T1D and T2D PRSs achieved a 0.72 AUC-ROC to discriminate between MODY and MODYx groups.

Interpretation:

The use of PRSs can help prioritizing MODYx cases who are more likely to have a high polygenic burden from those with low polygenic risk in which more comprehensive studies to find a causal mutation such as whole-exome, or whole-genome sequencing would be recommended.

Juraj Stanik

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Poster No: 53

INCIDENCE AND GENETIC BACKGROUND OF PERSISTENT CONGENITAL HYPERINSULINISM IN SLOVAKIA

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Congenital hyperinsulinism (CHI) is the most common cause of the persistent hyperinsulinemic hypoglycemia in children and occurs in approximately 1 in 50,000 live births. At least 11 known monogenic forms and several syndromes have been associated with CHI. **The aim of** this study was to evaluate incidence and genetic background of persistent CHI in Slovakia.
Patients and methods: Based on the data from the nationwide DIABGENE database of children with persistent hyperinsulinemic hypoglycemia, 28 children were diagnosed with CHI during the 2005-2022 years. DNA analysis of the most common CHI genes was performed. Incidence of CHI was calculated using the Slovak demographic data.
Results: Incidence of CHI in Slovakia is 1 in 39 217 live births. Genetic cause of CHI was identified in 12 children (42%). The most common were mutations in *ABCC8* (n=7) gene, followed by variants in *KCNJ11* (n=2) and *HNF4A* (n=2) genes. Five of six patients with a diazoxide-resistant form of CHI had an *ABCC8* or *KCNJ11* mutation. Three of these patients had focal form of CHI based on the paternally inherited recessive mutation and underwent partial pancreatectomy. One patient was identified with Beckwith-Wiedemann syndrome.
Conclusions: CHI is a rare disease with nation-wide incidence in Slovakia of 1:39 217 over the last 18 years. Genetic cause was identified in 42% of the patients; mutations in *ABCC8* gene were the most prevalent. The type of mutation determinates the most appropriate management strategy of these patients including pancreatic surgery.

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Poster No: 54

Characterizing 99 candidate genes for a role in MASLD using CRISPR/Cas9 and *in vivo* imaging

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INTRODUCTION: Steatotic liver disease (SLD) is often associated with metabolic dysfunction (MASLD) and can progress to steatohepatitis, cirrhosis and hepatocellular carcinoma. Genome-wide association studies (GWAS) have identified numerous loci that are associated with MASLD-related traits, but informative models to functionally characterize candidate genes are lacking. Here, we validate zebrafish larvae as a model system and characterize the role of 99 candidate genes.
METHODS: Liver fat was visualized in 10-day-old transparent zebrafish larvae using a dye and live fluorescence microscopy, followed by image analysis using deep learning-based neural networks. For validation, we compared liver fat in larvae with/without a metabolic challenge (n=721), treatment with rosiglitazone (n=865), or CRISPR/Cas9-induced mutations in *MTARC1* (n=383) or *GPAM* (n=307). Next, we jointly targeted all zebrafish orthologues of 99 human genes (one-by-one) using CRISPR/Cas9 (n>16,000).
RESULTS: On average, 5 days of overfeeding results in 1.7-fold more liver fat (beta±SE 0.49±0.10 SD units); 4% extra cholesterol in 1.4-fold more liver fat (0.61±0.10); and 3% glucose in 2.2-fold more liver fat (1.35±0.10). In challenged larvae, 10 or 25μM rosiglitazone for 5 days results in 40% less liver fat (-0.25±0.09). Finally, mutations in *MTARC1* and *GPAM* result in 6% less (-0.28±0.14) and 9.5% less (-0.56±0.24) liver fat. Finally, 15 of 99 perturbed genes affect liver fat; 12 of these were previously implicated in liver fat in human or mouse; and 10 of these (83%) show directionally consistent effects across species.
INTERPRETATION: Systematically characterizing genes for a role in MASLD using zebrafish larvae can meaningfully pinpoint putative causal genes.

KEY WORDS: *genetic screen, zebrafish larvae,* MASLD*, translational genomics, deep learning.*

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Poster No: 55

A specific *de novo ACTB* variant is a novel cause of syndromic neonatal diabetes.

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Introduction
For 10% of individuals with diabetes diagnosed before 6 months (neonatal diabetes) the genetic aetiology is unknown. Our aim was to identify novel causes of neonatal diabetes.

Methods
We performed whole-genome-sequencing in 39 probands and their unaffected parents. Genes with *de novo* variants in ≥2 probands were followed-up.

Results
The *de novo ACTB* (p.Ser348Leu) variant was identified in two unrelated individuals. Both had diabetes onset soon after birth (1 and 8 days), low birthweight (-3.22SD and -3.98SD), and extra-pancreatic features (deafness and developmental delay in one; intestinal atresia in the other).

The same *ACTB* (p.Ser348Leu) variant was reported in six individuals in the literature; three had neonatal diabetes/hyperglycaemia and extra-pancreatic features similar to our probands (deafness in 2/6; developmental delay in 2/6; gastrointestinal atresia in 5/6). In total, 5/8 individuals with the *ACTB* (p.Ser348Leu) variant had neonatal diabetes/hyperglycaemia. None of the 41 cases with other *ACTB* pathogenic variants in the Human Gene Mutation Database had diabetes (P-value= 2.94×10^{-5}).

ACTB encodes β-actin, a ubiquitous protein essential for many cellular functions, including vesicle-mediated transport and gene regulation. Further studies are needed to establish how this *ACTB* variant affects beta-cell development and/or function resulting in neonatal diabetes.

Interpretation
We identified a specific *de novo ACTB* variant in 2 probands with neonatal diabetes. The same *ACTB* variant was also previously reported in 3 additional individuals with syndromic neonatal diabetes/hyperglycaemia. These results suggest a mutation-specific mechanism and establish the *ACTB* (p.Ser348Leu) variant as a novel cause of neonatal diabetes.

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Poster No: 56

Melas Syndrome: A Case Report:

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A 43-year-old woman was referred for an endocrine genetic consultation due to a diagnosis of diabetes around the age of 30, early-onset sensorineural hearing loss, and premature ovarian insufficiency. The patient's mother, has also been diagnosed with diabetes, hearing impairment and stroke-like episodes.

Given the family history and the patient's clinical presentation, genetic testing was preformed, revealing a mitochondrial DNA mutation M3243 A>G associated with MELAS syndrome (Mitochondrial Encephalopathy, Lactic Acidosis, and Stroke-like Episodes) with a heteroplasmy level of 19%.

Based on the genetic findings, a metabolic workup was initiated, leading to the recommendation of supplementing with ubiquinol, citrulline, arginine, taurine, riboflavin, and alpha-lipoic acid. Medications capable of inducing lactic acidosis, such as metformin and statins, were discontinued. SGLT2 inhibitors were also stopped due to concerns about ketoacidosis.

The patient received guidance on emergency arginine therapy in suspected stroke-like episodes, characterized by altered consciousness, focal deficits, or seizures. Furthermore, comprehensive education on metabolic crises triggered by infections, psychological stress, or prolonged fasting was provided, emphasizing the importance of seeking medical attention for any changes in her baseline or cognitive status. The significance of updating healthcare providers on her medical condition before any surgical intervention was stressed.

Genetic counseling was recommended for first-degree relatives. This case underscores the intricate interplay between mitochondrial disorders and endocrine manifestations, emphasizing the importance of a multidisciplinary approach for accurate diagnosis and management.

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Poster No: 57

Phenotypic variation associated with inactivating *GCK* variants

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Introduction

Heterozygous inactivating variants in *GCK* cause stable and mild fasting hyperglycaemia. Different variants have distinctive *in vitro* effects on GCK enzyme activity, but the variation in the human phenotype has been little studied. We aimed to study the interplay of the variants and other factors determining the glucose levels in individuals.

Methods

We investigated *GCK* variants (classified as pathogenic or likely pathogenic) identified in at least three carriers and three non-carrier relatives in the FINNMODY/Botnia study. We assessed how variants and other factors modulate fasting plasma glucose (FPG), and for a subgroup, 2-hr plasma glucose (2PG) during an OGTT.

Results

The preliminary analyses of five variants (49 carriers, 22 non-carriers) suggest that each variant has a distinct effect on FPG (effect 1.17-2.24 mmol/l, FPG range 5.1-9.7 mmol/l) and 2PG (effect 1.19-2.70 mmoL/l, 2PG range 4.4-14.5 mmol/l). Among the carriers, FPG and 2PG were strongly correlated (p = 0.000676), and fasting insulin and C-peptide were more strongly correlated with the difference between the actual and the linear-model predicted FPG than the FPG alone – highlighting the influence of factors beyond GCK in modulating insulin response. HbA1c correlated more strongly with FPG than 2PG. There was a significant association between 2PG and blood pressure, and, using follow-up data, a significant association between FPG and waist circumference.

Interpretation

On top of the *GCK* variant, individual factors seem to modify the glucose level. The results warrant research on genetic and lifestyle factors associated with T2D modulating the metabolic outcome.

Rebecca Myers

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Poster No: 58

Children with syndromic diabetes should be considered for monogenic diabetes testing

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Introduction:

Genetic testing in childhood-onset diabetes currently targets MODY or rare genetic syndromes. We aim to determine whether genetic testing should be routinely recommended for children with diabetes and any additional non-autoimmune features (syndromic diabetes) and if biomarkers can help select children for testing.

Methods:

We studied 183 children diagnosed with diabetes and additional non-autoimmune features from predominantly non-European countries. We measured islet autoantibodies and 10-variant T1DGRS. We analysed all known dominant and recessive genetic causes of monogenic diabetes (n=58) using targeted next-generation sequencing.

Results:

33% (61/183) of children had monogenic diabetes. 84% were recessive causes with variants in *WFS1* (46%), *SLC19A2* (12%) and *SLC29A3* (12%) being most common. Monogenic and non-monogenic cases have similar age of diagnosis (7.4 vs 6, p=0.1) and BMI z-score (-0.08

vs -0.41, p=0.3). However, monogenic cases are more likely to have parental consanguinity (62% vs 19%, p=0.01) and additional features affecting multiple organ systems (44% vs 22%, $p<10^{-5}$). Only 56% (32/57) displayed typical phenotypical features of their respective genetic syndrome.

48% of islet autoantibody-negative cases had monogenic diabetes compared to 3% of islet autoantibody-positive cases ($p<10^{-7}$). Similarly, children with low T1DGRS (<50th centile of T1D population) compared to high T1DGRS (≥50th centile) are more likely to have monogenic diabetes (41% vs 5% $p<10^{-6}$).

Interpretation:

Change in current clinical practice is required to ensure all children with syndromic diabetes are considered for monogenic diabetes testing, particularly those from populations with high rates of consanguinity. Islet autoantibodies and T1DGRS help prioritise patients for genetic testing.

Raymond Kreienkamp

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Poster No: 59

Type 1 Diabetes Polygenic Scores Improve Diagnostic Accuracy in Pediatric Diabetes

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Introduction: Classifying pediatric diabetes type accurately is integral to providing optimal treatment. Yet, many cases of pediatric diabetes are still misclassified, including 80% of monogenic diabetes cases. New tools are needed to help clinicians classify pediatric diabetes type. In recent years, two type 1 diabetes (T1D) polygenic scores have been developed (Sharp 2018; Onengut-Gumuscu, 2019), utilizing genetics to differentiate T1D from other forms of diabetes.

Methods: To assess whether these tools might be helpful in clinical practice, we applied these scores to a group of pediatric patients (n=1870) with DNA sequencing data available in the Boston Children's Hospital PrecisionLink Biobank, including 95 individuals with a T1D diagnosis.

Results: Patients with a clinical diagnosis of T1D had higher scores compared to controls (Wilcoxon rank-sum $p<0.00001$ for both scores). However, within the T1D group, four individuals had scores comparable to controls (less than the 5th percentile for T1D and less than the 50th percentile for the population). In one individual, the provider had noted that the patient "may have type 2 diabetes despite…the presence of pancreatic autoantibodies but this is still hard to determine completely." The others had subtle clinical features of atypical diabetes but had no documentation of monogenic diabetes testing having occurred (not all patients follow at Boston Children's). We now aim to determine if those with low scores had a pathogenic variant in known diabetes-causing genes.

Interpretation: These studies demonstrate that T1D polygenic scores may have routine clinically applicability and aid in the diagnosis of pediatric diabetes.

Word Count: 248

Matthew Wakeling

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Poster No: 60

Clustering analysis of non-coding *de novo* variants to identify novel regulatory disease associations.

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Introduction

Beta-cell disallowed genes are specifically repressed in beta-cells but abundantly expressed across other cell and tissue types. Disruption of a regulatory region of the beta-cell disallowed gene *HK1* has recently been shown to cause congenital hyperinsulinism (CHI) by causing aberrant expression of *HK1* in patient beta-cells. To discover new genetic causes of CHI we searched for variants that might disrupt the regulation of 104 beta-cell disallowed genes.

Methods

We performed WGS on 104 unsolved CHI trios, plus 145 controls (including solved cases). We searched for *de novo* copy number variants (CNVs) using in-house software, and *de novo* single nucleotide variants and indels using DeNovoCNN, within 1 million base-pairs of 104 genes previously reported to be repressed in beta-cells from 3 mouse studies, plus *HK1*. We identified clusters of *de novo* variants within 100bp windows.

Results

27 clusters of *de novo* variants were found. The biggest cluster was the known *HK1* regulatory region, with 9 variants found, all in solved CHI patients. Only four clusters (of two patients each) contained solely unsolved CHI patients. Closer inspection of the IGV plots suggested these were likely sequencing errors in short tandem repeat regions.

Interpretation

Cluster analysis of *de novo* variants in non-coding regions highlights the known *HK1* region, showing the potential of the method for identifying regulatory causes of disease. Beta-cell disallowed genes remain a prime target for CHI research, but this analysis did not identify further likely disease-causing regions clustering near the beta-cell disallowed genes reported across 3 mouse studies.

Carolyn McGrail

University of California, San Diego

Poster No: 61

Development of a multi-ancestry T1D genetic risk score to characterize genomic changes in the pancreas

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Introduction

Genetic risk scores (GRS) for type 1 diabetes (T1D) have been largely developed in individuals of European ancestry, making it difficult to integrate multi-ancestry data to determine changes associated with T1D genetic risk.

Methods

To address this challenge, we developed a multi-ancestry GRS using a comprehensive set of 121 T1D risk variants at the MHC locus and genome-wide identified in both Europeans and African Americans. We then used this T1D GRS to examine the effect of genetic risk on genomic changes in the pancreas using a cohort of mixed ancestry individuals from the Network for Pancreatic Organ donors with Diabetes (nPOD) biorepository. We generated and processed single cell genomics (RNA-seq, ATAC-seq) data from 64 cryopreserved pancreatic tissues from nPOD.

Results

This 121-variant T1D GRS was highly predictive of T1D in both Europeans (AUC= 0.891) and African Americans (AUC=0.861), and we generated a T1D percentile scale separately for each ancestry to enable comparisons across multi-ancestry data. We then determined genomic profiles of each cell type associated with T1D polygenic risk using the T1D GRS which revealed increased cytokine-associated processes in ductal cells and decreased enzyme secretion signaling in acinar cells in high T1D genetic risk.

Interpretation

The use of the multi-ancestry GRS will enable analysis of mixed ancestry cohorts which will provide insight into disease mechanisms in at-risk individuals.

Roohia Khanam

Forman Christian College

Poster No: 62

Leptin-signaling deficiency is associated with remission in osteogenesis and increased oxidative stress

Roohia Khanam[1], Qasim M Janjua[2], Jaida Manzoor[3], Amélie Bonnefond[4,5,6], Sadia Saeed[4,5,6], Philippe Froguel[4,5,6], and Muhammad Arslan[1]

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Introduction: Obesity has been shown to impact bone metabolism. Among other regulatory factors, adipocyte-derived hormone leptin, and ROS have been implicated in bone turnover. Few studies relate to the assessment of bone metabolism in patients with monogenic forms of obesity. Here, we investigate bone impairment using bone turnover and oxidative stress biomarkers in children with severe obesity with biallelic loss-of-function mutations in *LEP, LEPR, or MC4R* genes.

Methods: This cross-sectional study included 41 study subjects 1-16 years old, with a BMI SDS >3, previously identified with pathogenic mutations in *LEP*, *LEPR,* and *MC4R,* and 16 age-matched normal-weight controls. Bone-turnover markers osteocalcin (OC), osteopontin (OPN), and sclerostin (SOST) were measured by multi-analyte profiling to evaluate bone health. Serum leptin, malondialdehyde (MDA), 8-hydroxy-2'-deoxyguanosine (8-OHdG), and glutathione (GSH), were assessed by ELISA.

Results: Serum concentrations of bone formation markers OC and OPN were significantly lower in patients with LEP or LEPR deficiency whereas those of bone resorption biomarker SOST, were elevated. In contrast, osteogenic markers were significantly increased in subjects with MC4R deficiency. Serum MDA and 8-OHdG were significantly higher and levels of antioxidant GSH lower in children with deficient leptin signaling (LEP, LEPR) compared to MC4R deficient and normal control values.

Interpretation: The study confirms the pivotal role of leptin in osteogenesis and maintenance of bone homeostasis. In the absence of leptin signaling, elevated ROS levels may further compromise osteogenesis and exacerbate bone resorption. Use of bone biomarkers provides a convenient and sensitive method for evaluation of bone health in children with obesity.

Jacques Murray Leech

University of Exeter

Poster No: 63

Polygenic Background is an Important Determinant for MODY Clinical Phenotype

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Introduction:

Pathogenic variants are key drivers of MODY phenotype, however it is unknown whether polygenic background contributes to the phenotype as well. We aimed to assess whether polygenic risk of diabetes-related traits contribute to or modify the MODY phenotype.

Methods:

We analysed 1,885 genetically confirmed MODY probands referred from routine clinical practice in the UK (*HNF1A/4A*=844, *GCK*=709, Others=332). We analysed TOPMed-imputed array genotypes and constructed polygenic risk scores (PRS) for type 2 diabetes (T2D), fasting glucose (FG) and 10 other diabetes-related traits. We compared PRS distributions in MODY cases to 7,962 controls and 5,109 T2D cases. We assessed association of each PRS with age of diagnosis, HbA1c, BMI and insulin treatment in MODY cases.

Results:

T2DPRS of *HNF1A/4A*-MODY was significantly higher than controls but lower than T2D cases (mean 0.11 vs -0.26 vs 0.34, $p<0.0001$) whereas FGPRS was similar to controls. Partitioned T2D scores demonstrated beta cell SNPs were the only cluster significantly different from controls ($p<0.0001$).

GCK-MODY cases had higher FG/HbA1cPRS than controls ($p<0.0001$) but not T2DPRS.

In *HNF1A/4A*-MODY, one SD increase in T2DPRS was associated with 0.92y earlier diagnosis of diabetes, 0.17% higher HbA1c, 0.37 kg/m² higher BMI and 24.7% increase in the odds of insulin treatment. Other MODY subtypes that causes diabetes by insulin deficiency had similar results. Additionally, one SD increase in HbA1cPRS was associated with 0.08% higher HbA1c in *GCK*-MODY.

Interpretation:

Both monogenic variants and polygenic burden contribute to the MODY phenotype, differing by subtype. Polygenic risk helps explain variable phenotypes of monogenic diabetes.

Shenali Amaratunga

Charles University and University Hospital Motol, Prague

Poster No: 64

Genetic and clinical spectrum of congenital hyperinsulinism in the Czech Republic: 10 years of investigation

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Introduction

Congenital hyperinsulinism (CHI) is a heterogeneous genetic condition leading to uncontrolled insulin secretion irrespective of blood glucose levels. Genetic testing of Czech patients with the clinical diagnosis of CHI began 10 years ago. This study aims to describe the prevalence of CHI subtypes among referred patients and define clinical characteristics.

Methods

Genetic testing was performed by Sanger sequencing of *ABCC8* and *KCNJ11* genes followed by targeted NGS of 52 (63) genes since 2018. Patient data were obtained from clinical questionnaires.

Results

The genetic cause of CHI was confirmed in 28/102 (27.4%) patients (14 females, 9 transient CHI): 20 had pathogenic variants in the *ABCC8* gene, two in *KCNJ11*, *HNF1A* and *HNF4A*, respectively, one in *GCK* and one had heterozygous variants in both *ABCC8* and *KCNJ11* genes. CHI was diagnosed within the first four days of life in 96% of positive patients. One third was born macrosomic. Median glucose and insulin levels in critical sample were 1.7 (1.4-2.0) mmol/l and 22.2 (11.7-37.4) mIU/l. A tenth of patients required only glucose infusions to maintain normoglycaemia, while 29% responded to diazoxide, 29% were on octreotide, 14% on sirolimus, and 18% obtained combination of two or more pharmacological agents. Focal HH was confirmed in 58.8% (10/17) tested patients. Two patients underwent partial pancreatectomy.

Interpretation

Variants in 5 different genes have been observed in CHI patients, with *ABCC8* gene variants being most prevalent. A timely, personalised and complex approach including genetic testing, imaging and precise treatment is required in such patients.

Alys Ridsdale

University of Exeter

Poster No: 65

Title: Prevalence and impact of pathogenic *G6PD* variants on HbA1c and type-2-diabetes diagnosis in UK ethnic-groups

Alys M. Ridsdale[1], Katherine G. Young[1], Harry D. Green[1], Robin N. Beaumont[1], Andrew R. Wood[1], Inês Barroso[1]* and Susan Martin[1]*

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Glucose-6-phosphate dehydrogenase (G6PD) deficiency is an X-linked disorder affecting 400M individuals globally. Common in African and Asian populations due to its protective effect against malaria, it is rare in Europe. Variants rs1050828-T and rs5030868-A are associated with up to ~5-10mmol/mol lower glycated haemoglobin (HbA1c) levels, independently of glycaemia. Since HbA1c is the diagnostic test for type 2 diabetes (T2D), *G6PD* variant-carriers may experience delays in T2D diagnosis. We aimed to investigate the prevalence of pathogenic *G6PD* variants in UK ethnic groups, and understand their impact on HbA1c and T2D age-at-diagnosis.

Analysing whole-exome sequence and health record data of >500,000 individuals, aged 40-69, in UK Biobank, we identified pathogenic *G6PD* variants (December 2023 ACMG classifications). We used PLINK to retrieve genotypes, and excluded individuals with any diabetes diagnosis, or HbA1c-impacting condition (pregnancy, or 6-weeks post-partum, N=360,399). Using a dominant model and Student's t-test, we assessed the impact of carrier-status on HbA1c and random glucose, by self-reported ethnicity.

We identified 214 previously-characterised *G6PD* variants, excluding rs1050828-T and rs5030868-A. Fifty-seven were classified pathogenic/likely pathogenic and present in 2,494 carriers. Pathogenic-variant carrier-prevalence ranged from 5.2% (Asian females) to 0.24% (White males), with 99.3% lacking a G6PD deficiency diagnosis. Male-carriers had ~9.4mmol/mol lower HbA1c levels (median=27.9mmol/mol, IQR=30.1-26.6mmol/mol) compared to non-carriers (median=37.3mmol/mol, IQR=39.5-34.5mmol/mol), while random glucose was indistinguishable (carriers median=4.9mmol/l, IQR=5.3-4.7mmol/l; non-carriers median=4.9mmol/l, IQR=5.3-4.6mmol/l). Results were similar in female-carriers but with more modest effects on HbA1c.

G6PD variants beyond rs1050828-T and rs5030868-A lower HbA1c independently of glycaemia and may contribute to ethnic-specific T2D diagnosis inequalities.

Aminata Cisse

University of Exeter

Poster No: 66

Title: Glycemic and non-glycemic determinants of HbA1c during vs. outside pregnancy

Authors:

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Introduction: Glycated hemoglobin (HbA1c) assesses glucose control in early pregnancy for women with preexisting diabetes. HbA1c is influenced by changes in glucose regulation and red blood cell characteristics, therefore its usefulness in pregnancy is unclear. We aimed to compare pregnancy vs. non-pregnancy associations of HbA1c with glycemic and non-glycemic measures and genetic scores (HbA1c-gGRS; HbA1c-ngGRS).

Methods: We included 787 pregnant and 376 non-pregnant women from the EFSOCH and EXTEND cohorts, respectively (British European origin, 18-45yrs, without known diabetes). We used linear regression to determine proportions of HbA1c variance explained by fasting glucose, hemoglobin, HbA1c-gGRS and HbA1c-ngGRS. Then, we examined associations between HbA1c and each GRS during and at median 4.83yr post-pregnancy in EFSOCH.

Results: At equal age, BMI, fasting glucose and hemoglobin level, pregnant women had lower HbA1c than non-pregnant women (β[95%CI] =-0.44% [-0.50;-0.38]). Variance in HbA1c explained by fasting glucose and hemoglobin was higher in pregnant (11.2% and 3.2%) than in non-pregnant women (10.4% and 2.5%). While HbA1c-ngGRS explained less variance in pregnancy (0.5%) than post-pregnancy (1.80%), and HbA1c-gGRS did not explain any variance. Associations between HbA1c and each GRS showed no detectable differences, albeit with wide confidence intervals: HbA1cgGRS=0.21 [-0.16;0.58] pregnancy vs. 0.11 [-0.28;0.50] post-pregnancy; HbA1c_ngGRS=0.19 [-0.00;0.38] pregnancy vs. 0.30 [0.09;0.51] post-pregnancy.

Interpretation: We observed significant HbA1c variation during vs. outside pregnancy. Further analyses in larger samples are needed to better understand the contribution of glycemic and non-glycemic factors as these have implications for the suitability of HbA1c reference ranges and its use for diabetes management in pregnancy.

Vincent Pascat

University of Lille

Poster No: 67

Genetic predisposition between type 2 diabetes and blood pressure highlights insulin resistance and central obesity.

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Introduction: Type 2 diabetes (T2D) and elevated blood pressure (BP, including systolic [SBP] and diastolic [DBP]) are complex frequently co-occurring conditions. Understanding shared genetic factors between them could bring insight into the underlying pathophysiological processes.

Methods: We dissected the effects of 563 T2D and 999 BP variants established using genome-wide association studies (GWAS), by constructing polygenic score (PGS) in a set of 457,386 European individuals from UK Biobank (UKB). We gathered Z-scores from GWAS on 49 endophenotypes and utilised them to cluster 1,542 genetic variants into distinct pathophysiological processes and investigated cluster-specific PGSs for comorbidity. We performed bi-directional two-sample Mendelian Randomization (MR) to explore causal relationships between T2D/BP. We used GTEx expression quantitative trait loci (eQTL) in 49 tissues to identify co-localisation of these variants.

Results: T2D overall PGS was associated with risk of elevated BP, and vice versa (P-values ≤ 0.0167). MR suggested that T2D has an heterogenous causal effect on BP. Partitioning genetic variants defined five clusters of different pathogenetic processes, whereby Cluster2 featured individuals with metabolic syndrome characteristics, *i.e.,* central obesity, insulin resistance and shorter stature. MR using Cluster2 variants revealed a circle of causality between DBP, T2D, and SBP, with each increasing risk of comorbidity ($OR_{\text{IVW DBP}\rightarrow\text{PP through Cluster2}}[95\%\ \text{CI}] = 1.04[1.02 - 1.06]$; $\beta_{\text{IVW T2D}\rightarrow\text{SBP through Cluster2}}[\text{SE}] = 1.987\ [0.278]$, P-values $\leq 1.86 \times 10^{-5}$). Cluster2 co-localised genes had enriched co-expression in adipose subcutaneous, thyroid and artery tibial tissues ($PP.H4.abf > 0.8$).

Interpretation: Clustering SNPs by pathogenetic process highlighted the importance of central obesity and insulin resistance into causal effect of T2D leading to altered BP.

Jasmin Hopkins

University of Exeter

Poster No: 68

Non-coding regulatory variants in *HK1* cause congenital hyperinsulinism with a broad phenotypic spectrum

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Introduction

Congenital hyperinsulinism (HI) is a monogenic disorder characterised by the inappropriate secretion of insulin during hypoglycaemia. We recently discovered non-coding, regulatory variants within Hexokinase 1 (*HK1*) as a novel cause of HI. These variants cause HK1 to be aberrantly expressed in the pancreatic beta cells. We investigated the phenotype associated with this novel subtype of disease by screening a large cohort of genetically unsolved individuals with HI.

Methods

We screened the *HK1* regulatory region in 1,091 probands referred for HI genetic testing. Variants in the known HI genes had been excluded in all individuals. Family members were tested when a variant was identified, and clinical features were collated.

Results

We identified 28 different variants within the *HK1* regulatory region in 59 individuals from 55 families (5%). All variants were absent from control datasets. Birth weight z-score ranged from -2.66 to 3.89, with 30% (n=15/50) born large for gestational age, indicating increased insulin secretion *in utero*. Age at diagnosis ranged from birth to 2.4 years with 42% (n=25/59) diagnosed outside the neonatal period. At follow-up (median age 6 years), 88% (n=49/59) were medically managed, of these 37 individuals were treated with diazoxide only. 17% (n=10/59) were not responsive to diazoxide and required subtotal pancreatectomy. 8 probands had inherited the variant from an unaffected parent, indicating reduced penetrance.

Interpretation

Variants in the *HK1* regulatory region were identified in ~5% of probands with genetically unsolved HI. The phenotype ranged from early-onset, diazoxide-unresponsive HI requiring subtotal pancreatectomy to being clinically unaffected in adulthood.

Jana Soenksen

University of Exeter

Poster No: 69

Fine-mapping of glycaemic trait loci: combining functional annotation and multi-trait methods improves resolution

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Introduction: The Meta-Analysis of Glucose and Insulin-related traits Consortium (MAGIC) identified 242 loci associated with glycaemic traits, 2h-Glucose (2hGlu), fasting insulin (FI), glycated haemoglobin (HbA1c), and fasting glucose (FG). Despite fine-mapping efforts, the causal variant(s) at most loci remain unknown. Modelling multiple traits and integrating functional annotations have been shown separately to improve fine-mapping resolution. This study aims to combine these techniques to reduce the list of potential causal variants.

Methods: Employing fGWAs v.0.3.6, we constructed a model incorporating 28 static annotations and 32 cell-type specific stretch enhancers (StrE). Resulting enrichments were used to calculate each SNP's prior probability of causality. We used FINEMAP v1.4 to compute posterior probabilities (PP) and credible sets accounting for 99% PP of causality (99CS) for 211 locus-trait associations. Results were used in multi-trait fine-mapping of 50 loci associated with multiple traits (110 locus-trait associations) using flashfm with default parameters, except TOdds=0.25.

Results: Static annotation enrichments, e.g. coding or conserved regions, were found across FG, 2hGlu, and HbA1c. FG and 2hGlu also had enrichments of islet StrE; FI was enriched in adipose-specific StrE. Comparing annotation-informed single-trait to agnostic fine-mapping, the median 99CS size improved from 67 to 51 variants ($p=6.96x10^{-12}$). Multi-trait annotated fine-mapping further reduced the median 99CS size from 50.5 to 14.5 variants ($p=2.69x10^{-18}$). Missense variants (PP >0.5) were identified in *GCKR, GIPR, SLC30A8, SLC2A2, PFKM, CERS2, MLXIPL*, and *ZFP36L2*; all but *ZFP36L2* have established animal models with metabolic phenotypes.

Interpretation: Combining multi-trait and annotation-informed fine-mapping refines causal variant identification at glycaemic trait loci.

Agata Juszczak

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Poster No: 70

New MODY clinic - the same challenges

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Introduction

Maturity onset diabetes of the young (MODY) is estimated to account for 0.5-1.2% of the diabetes population. An early diagnosis allows personalised treatment and good outcomes. Despite 3 decades from discovery of most common genes causing MODY, it remains underdiagnosed and genetic diagnosis is established on average more than 10 years after the diagnosis of diabetes.

Methods

We reviewed hospital records of all patients referred to our MODY clinic since it started 18 months ago. The aim was to establish outcomes of this clinic including number of patients selected for genetic testing, time to genetic diagnosis and treatment change.

Results

We have received 133 referrals from June 2022 – Jan 2024. This included 25 individuals with already genetically confirmed MODY and 112 new referrals. Diagnosis was changed in 42.3% (n=56) of patients and 32% (n=42) proceeded to the genetic testing. We diagnosed MODY in 17 individuals (40% of genetically tested). The mean time from diagnosis of diabetes to the genetic diagnosis was 13 (0-54) years and mean BMI was 25 (30% of patients BMI>27). The insulin was stopped in 9 patients and all diabetes treatment was stopped in 5 individuals.

Conclusions

The genetic diagnosis of MODY remains significantly delayed, which supports dedicated MODY clinics and strengthens the role of genetic diabetes nurse. Ongoing education at different levels of medical education is needed to improve results.

Significant increase in the prevalence of obesity should make us consider patients with above normal BMI when strong suspicion of MODY exists.

Agata Juszczak

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Poster No: 71

Dual diagnosis of GCK-MODY and Type 1 diabetes

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Introduction

GCK-MODY accounts for 30-60% of MODY cases. Inactivating heterozygous mutations in *GCK* lead to mild hyperglycaemia since birth and HbA1c usually not exceeding 64mmol/mol. GCK-MODY does not progress to cause complications of diabetes and does not require treatment except for pregnancy when mum carries the mutation, but baby does not.

Case Study

We report 36-year-old woman diagnosed with gestational diabetes during her first pregnancy aged 21 when treated with insulin therapy. Following pregnancy, she underwent an oral glucose tolerance test (OGTT) which was consistent with persistent diabetes (2hour glucose of 14.9mmol/l) and HbA1c of 73mmol/mol. She was given diagnosis of Type 1 diabetes and remained on insulin therapy. In her second pregnancy, genetic testing was triggered and confirmed GCK-MODY due to *GCK* heterozygous mutation (p.L146fs, c.435_436dup). Her GAD antibodies were elevated at 34 IU/ml with borderline ZnT8 antibodies so insulin was continued. At that point, she was referred to our Monogenic Diabetes Clinic to clarify which type of diabetes does she have to guide the treatment.

Her family history of diabetes was typical of monogenic diabetes with four generations involved. Her C-peptide was low at 71pmol/L with glucose of 13.2mmol/l, consistent with insufficient endogenous insulin production and together with positive GAD antibodies confirmed co-existing type 1 diabetes and GCK-MODY. Advise was given to continue basal-bolus insulin therapy.

Conclusion

It is possible for patients to receive a dual diagnosis of GCK-MODY and Type 1 diabetes or type 2 diabetes and treatment of the later should be advised.

Vasiliki Lagou

University of Surrey

Poster No: 72

Microbiome-wide association analysis for type 2 diabetes.

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Introduction: The composition of the gut microbiome is related to type 2 diabetes (T2D) risk. We characterised the differences in gut microbiome composition between individuals with T2D and without and investigated the role of lifestyle in these associations.

Methods: We evaluated 3,613 individuals of whom 65 had medical history of T2D and information about stool 16S rRNA sequencing along with accompanying questionnaires capturing lifestyle, dietary habits, and medical history. The association between the relative abundance (RA) of 79 bacterial genera and T2D was examined using microbiome-wide association analysis (MWAS) by MaAsLin2 and analysis of compositions of microbiomes with bias correction (ANCOM-BC) methods, for prevalent taxa >0.1. These models included multiple testing correction and adjustment for geographical region, age, gender and batch effect.

Results: Self-reported history of T2D inversely associated with longer sleep duration, yoga practicing, diet higher in fibre ($q<0.05$) and microbial alpha diversity ($p<0.05$). RA of three bacteria taxa were associated with type 2 diabetes ($q<0.05$) in both MWAS methods. RA of *Shigella* was higher in individuals with T2D, while RA of *Lachnospira*, *Terrisporobacter*, were lower. When we adjusted for T2D lifestyle confounding factors, butyrate producing bacteria *Lachnospira* showed inverse association with T2D status.

Interpretation: Lifestyle factors explained the association for two out of three taxa associated with T2D in this dataset, suggesting that they all should be considered for better understanding the role of lifestyle microbiome interplay in T2D.

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Vasiliki Lagou

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Poster No: 73

Multi-phenotype analysis reveals shared genetics between type 2 diabetes and colorectal cancer in UK Biobank

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Introduction: Genome-wide association studies (GWAS) have identified genetic loci for complex traits using the traditional univariate approach. The multivariate methods, including "reverse regression"-based SCOPA and MultiPhen, are more powerful over univariate models to detect multi-phenotype effects. These tools, however, support text-based formats only, limiting them from application on biobank-scale data. Here, we extended SCOPA software tool to a computationally efficient for large-scale data and evaluated its performance in a UK biobank-based multi-phenotype GWAS.

Methods: The extended version of SCOPA utilises BGEN in addition to GEN input files, while preserving all original features, including accommodation of both directly genotyped and imputed variants and model selection implementing the Bayesian Information Criterion (BIC). The performance of the BGEN-compatible version of SCOPA was evaluated in a multi-phenotype GWAS on type 2 diabetes (T2D) and colorectal cancer (CRC) in 487,409 UKBB individuals.

Results: We identified 133 independent loci jointly associated with T2D and CRC (two-phenotype model P-value<5×10^{-8}), including *POU5F1* and *CDKN2B-AS1*. Of these, 118 were novel as previously associated with only one outcome, such as *PEPD* for T2D or *COLCA1* for CRC. Dissection of the multi-phenotype associations based on BIC highlighted effects on both outcomes at 23 loci, of which 15 were considered novel as previously associated with either T2D only (*FAF1, PTGFRN, MIR4686, RPL12P33, NPM1P47, PEPD, APOC1, EYA2, CEBPB*) or CRC only (*LINC02257*, *R3HDM1*, *COLCA1/2*, *FMN1*, *CASC20*, *LINC01713*).

Interpretation: The multi-phenotype GWAS in large datasets enables dissection of shared genetic basis of correlated phenotypes. We illustrated the utility of the BGEN-format implementation in SCOPA to facilitate such analyses.

Brynmor Brunsdon-Håland

University of Bergen, Norway

Poster No: 74

RFX6-associated MODY in Norwegian diabetes population

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Introduction The RFX6 transcription factor is a crucial contributor to pancreatic islet development. Heterozygous protein truncating variants (PTVs) in the *RFX6* gene have recently been associated with MODY with reduced penetrance. We aim to investigate the prevalence of *RFX6* PTVs in the Norwegian diabetes population.

Methods We screened for PTVs in *RFX6* by Sanger or next-generation sequencing. Cases were selected from the Norwegian MODY Registry and 500 Norwegian blood donors served as controls. Samples from the Norwegian Childhood Diabetes Registry and the Norwegian Adult Diabetes Registry will be subsequently investigated.

Results Preliminary data upon diagnostic genetic testing for MODY and thereafter, screening of the Norwegian MODY Registry (1752 probands) identified eleven cases with the same truncating *RFX6* variant, namely c.348dup p.(Lys117Ter). MODY caused by the p.(Lys117Ter) variant comprises 2.7% of probands with a genetic diagnosis in this registry. The variant is not found in controls or in GnomAD.

Interpretation and future perspectives The p.(Lys117Ter) variant is enriched in the Norwegian MODY Registry compared to international and control cohorts. This may suggest a possible founder effect in the Norwegian population. We will employ haplotyping to assess potential familial relationships between these identified cases. Individuals harbouring this variant will be invited to clinical examination to obtain a better understanding of the associated phenotypes. An improved understanding of the clinical manifestations of these variants is important to deliver a precise diagnosis including optimal treatment, ultimately enhancing diagnostic accuracy and enabling personalised medicine.

Helena Murray

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Poster No: 75

Dried Blood Spots As A Simplified Sample Input For Generation Of A 10-SNP Type 1 Diabetes Genetic Risk Score: Improving Accessibility And Ease-Of-Use

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Introduction

Discrimination between Type 1 Diabetes (T1D) and other non-autoimmune diabetes is becoming increasingly challenging as traditional indicators (BMI/Age/Autoantibody status) are no longer reliable. A 10-Single Nucleotide Polymorphism (SNP) Type 1 Diabetes Genetic Risk Score (T1D-GRS) has been shown to be highly discriminative and aids in clinical diagnosis and prediction of disease progression. Generating this 10-SNP T1D-GRS using Randox Biochip Array Technology (BAT) has been shown to be quick, accurate and cost-effective. A method has been developed for home sample collection whilst eradicating the need for DNA extraction and quantification.

Methods

The assay combines established 10-SNP T1D-GRS BAT with a novel sample preparation and PCR protocol. Dried Blood Spot (DBS) samples were collected on Whatman 903 Protein Saver Cards and prepared using a Randox Blood Card Buffer. These processed DBSs are added directly to the PCR allowing for proprietary multiplex PCR and BAT protocol. 143 pre-characterised clinical samples (TaqMan, University of Exeter) were utilised to evaluate the assay.

Results

Of 1430 genotypes generated 99.8% concordance was observed and 140/143 (97.9%) corresponding T1D-GRSs were correct. Additionally, exogenous substances and DBS stability testing yielded 100% genotype and GRS concordance.

Interpretation

The use of DBS has been shown to maintain excellent assay performance. Use of a home sample collection kit will allow for accelerated turnaround time, greater accessibility to testing and reduced costs for the user. This could facilitate the use of T1D-GRS in combination with autoantibody testing for screening/prediction of type 1 diabetes, and for improved classification of diabetes.

Molly Endicott

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Poster No: 76

A pan-cancer investigation into the associations between diabetes mellitus and cancer type

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Introduction

Epidemiological studies have demonstrated that individuals with diabetes have an increased risk of several types of cancer including colorectal, breast and endometrial. However, the exact biological mechanisms responsible for these associations remain unclear. Our aim is to investigate the impact of diabetes on the mutational landscape of cancer using a pan-cancer approach.

Methods

We have explored the associations between cancer and diabetes in patients from the 100,000 Genomes Project. Our cohort (n = 13,577) consists of individuals diagnosed with cancer types including adult glioma, bladder, breast, colorectal, endometrial, haematological, hepatopancreatobilary, lung, melanoma, oral oesophageal, ovarian, prostate, renal, sarcoma and upper gastrointestinal. We used logistic regression to assess the effect of diabetes on cancer occurrence across the cohort and tested the impact of sex on these associations.

Results

We identified 7 cancer types that demonstrate a statistically significant association ($p < 0.05$) with diabetes in our cohort. Our investigation highlighted an increased risk of cancer in individuals with diabetes in 4 of the 7 cancer types (odds ratio: 1.14 – 2.04) and a decreased risk in the remaining 3 cancer types (odds ratio: 0.61 – 0.69). We have also investigated 5 cancer types which demonstrate associations with type 1 diabetes ($p < 0.05$) and 7 cancer types which demonstrate associations with type 2 diabetes ($p < 0.05$). Further investigation into sex specific differences showed that when analysis is split by sex, males and females highlighted a significant difference in the association between diabetes and certain cancers.

Interpretation

This study has provided a novel insight into sex-specific associations between cancer type and diabetes status, demonstrating that in this cohort males with diabetes are at a higher risk of colorectal cancer than females. This implies a sex-dependent influence of disrupted glycaemic environment on cancer risk which could have implications for tumour evolution.

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